09/719748

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=> d his

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     FILE 'STNGUIDE' ENTERED AT 16:20:51 ON 18 AUG 2005

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 16:21:28 ON 18 AUG 2005
L1        128381 S CALMODULIN
L2       2167794 S CALCIUM
L3          5710 S L1 (2W) L2
L4          1485 S L3 AND KINASE?
L5           149 S "DRP-1"
L6             1 S L3 AND L5
L7        712168 S APOPTOSIS OR (CELL(A)DEATH)
L8            66 S L3 AND L7
L9            48 DUP REM L8 (18 DUPLICATES REMOVED)
L10            0 S L9 AND "DAP(W)KINASE?"
L11          922 S DAP(2W)KINASE?
L12           30 S L5 AND L11
L13            9 DUP REM L12 (21 DUPLICATES REMOVED)
L14            2 S L4 AND "DAP"
                 E KIMCHI A/AU
L15          527 S E3
L16         1633 S L4 OR L5
L17           11 S L15 AND L16
L18            4 DUP REM L17 (7 DUPLICATES REMOVED)
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                   data from INPADOC
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=> s calmodulin
L1      128381 CALMODULIN

=> s calcium
L2     2167794 CALCIUM

=> s l1 (2w) l2
L3        5710 L1 (2W) L2

=> s l3 and kinase2
2 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
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"HELP COMMANDS" at an arrow prompt (=>).

=> s l3 and kinase?
L4 1485 L3 AND KINASE?

=> s "DRP-1"
L5 149 "DRP-1"

=> s l3 and l5
L6 1 L3 AND L5

=> d all

L6 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:811348 HCAPLUS
DN 132:46958
ED Entered STN: 24 Dec 1999
TI Cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-1** and
IN Kimchi, Adi
PA Yeda Research and Development Company Ltd., Israel; McInnis, Patricia A.
SO PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N009-12
ICS C12N001-20; C12N005-00; C12N015-00; C12Q001-68; C07H021-04; A61K038-51
CC 7-5 (Enzymes)
Section cross-reference(s): 1, 3, 13, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9966030	A1	19991223	WO 1999-US13411	19990615
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9944408	A1	20000105	AU 1999-44408	19990615
	GB 2354522	A1	20010328	GB 2001-660	19990615
	GB 2354522	B2	20040121		
PRAI	US 1998-89294P	P	19980615		
	WO 1999-US13411	W	19990615		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9966030	ICM	C12N009-12
	ICS	C12N001-20; C12N005-00; C12N015-00; C12Q001-68; C07H021-04; A61K038-51
WO 9966030	ECLA	C07K014/47A33; C12N009/12B1
GB 2354522	ECLA	C07K014/47A33; C12N009/12B1

AB A new protein kinase, DAP-Kinase related 1 protein (**DRP-1**), which is a novel homolog of DAP-kinase, has been isolated. and cDNA sequence and amino acid sequences of human **DRP-1** are reported. This novel calmodulin-dependent kinase is a cell death-promoting protein functioning in the biochem. pathway which involves DAP (death-associated protein)-kinase (e.g., forming a cascade of sequential kinases, one directly activating the other). Alternatively, the two kinases may operate to promote cell death in parallel pathways.
ST protein kinase DRP1 cDNA sequence cell death; DAP kinase related protein DRP1 sequence
IT Enzyme functional sites
(active; cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-**

1 and)
IT Enzyme functional sites
(apoptosis-inducing; cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP**-1 and)
IT **Calmodulins**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**calcium** complexes; cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP**-1 and)
IT Diagnosis
(cancer; cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP**-1 and)
IT Apoptosis
Cytoplasm
Drugs
Molecular cloning
Nucleic acid hybridization
Organ, animal
Protein sequences
cDNA sequences
(cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-1** and)
IT mRNA
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-1** and)
IT Antibodies
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); NUU (Other use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-1** and)
IT Antisense RNA
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-1** and)
IT Antibodies
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); NUU (Other use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)
(monoclonal; cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP**-1 and)
IT 252751-93-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid sequence; cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP**-1 and)
IT 252749-39-6 252752-17-3
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(amino acid sequence; cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP**-1 and)
IT 7440-70-2D, Calcium, calmodulin complexes, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-1** and)
IT 252866-91-4, DAP-kinase related protein kinase **DRP-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-1** and)
IT 215819-61-7, DNA (human DAP-kinase related protein kinase **DRP-1** cDNA plus flanks)
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-1** and)
IT 252752-23-1 252752-33-3 252752-35-5
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(nucleotide sequence; cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-1** and)
IT 252911-09-4, 1: PN: WO9966030 SEQID: 13 unclaimed DNA 252911-10-7, 2: PN: WO9966030 SEQID: 14 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-1** and)
IT 252911-11-8 252911-12-9 252911-13-0 252911-14-1 252935-11-8
RL: PRP (Properties)
(unclaimed protein sequence; cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-1** and)
IT 252868-22-7 252868-23-8 252868-24-9 252868-25-0 252868-26-1
RL: PRP (Properties)
(unclaimed sequence; cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-1** and)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Deiss; Genes & Development 1995, V9, P15 HCAPLUS
(2) Hillier; The WashU-Merck Project 1995
(3) Yeda Research and Development Co Ltd; WO 9510630 A 1995 HCAPLUS

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FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 16:21:28 ON 18 AUG 2005
L1 128381 S CALMODULIN
L2 2167794 S CALCIUM
L3 5710 S L1 (2W) L2
L4 1485 S L3 AND KINASE?
L5 149 S "DRP-1"
L6 1 S L3 AND L5

=> s apoptosis or (cell(a)death)
5 FILES SEARCHED...
L7 712168 APOPTOSIS OR (CELL(A) DEATH)

=> s l3 and l7
L8 66 L3 AND L7

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9 48 DUP REM L8 (18 DUPLICATES REMOVED)

=> d 1-48 ibib ab

L9 ANSWER 1 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:83188 HCAPLUS
DOCUMENT NUMBER: 142:407498

TITLE: The importance of calcium influx, calpain and calmodulin for the activation of CaCo-2 **cell death** pathways by Clostridium perfringens enterotoxin
AUTHOR(S): Chakrabarti, Ganes; McClane, Bruce A.
CORPORATE SOURCE: Department of Molecular Genetics and Biochemistry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
SOURCE: Cellular Microbiology (2005), 7(1), 129-146
CODEN: CEMIF5; ISSN: 1462-5814
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB CaCo-2 cells exhibit **apoptosis** when treated with low doses of C. perfringens enterotoxin (CPE), but develop oncosis when treated with high CPE doses. This study reports that the presence of extracellular Ca2+ in treatment buffers is important for normal activation of both those **cell death** pathways in CPE-treated CaCo-2 cells. Normal development of CPE-induced **cell death** pathway effects, such as morphol. damage, DNA fragmentation, caspase activation, mitochondrial membrane depolarization and cytochrome c release, was strongly inhibited when CaCo-2 cells were CPE-treated in Ca2+-free buffers. When treatment buffers contained Ca2+, CPE caused a rapid increase in CaCo-2 cell Ca2+ levels, apparently because of increased Ca2+ influx through a CPE pore. High CPE doses caused massive changes in cellular Ca2+ levels that appear responsible for activating oncosis, whereas low CPE doses caused less perturbations in cellular Ca2+ levels that appear responsible for activating **apoptosis**. Both CPE-induced **apoptosis** and oncosis were found to be calmodulin- and calpain-dependent processes. As Ca2+ levels present in the intestinal lumen resemble those of Ca2+-containing treatment buffers used in this study, perturbations in cellular Ca2+ levels and calpain/calmodulin-dependent processes are also probably important for inducing enterocyte **cell death** during CPE-mediated gastrointestinal disease.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 48 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004355285 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15145946
TITLE: Novel functional interaction between the plasma membrane Ca2+ pump 4b and the proapoptotic tumor suppressor Ras-associated factor 1 (RASSF1).
AUTHOR: Armesilla Angel L; Williams Judith C; Buch Mamta H; Pickard Adam; Emerson Michael; Cartwright Elizabeth J; Oceandy Delvac; Vos Michele D; Gillies Sheona; Clark Geoffrey J; Neyses Ludwig
CORPORATE SOURCE: Division of Cardiology, University of Manchester, Manchester M13 9PT, United Kingdom.
SOURCE: Journal of biological chemistry, (2004 Jul 23) 279 (30) 31318-28. Electronic Publication: 2004-05-15.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 20040720
Last Updated on STN: 20040922
Entered Medline: 20040921

AB Plasma membrane **calmodulin**-dependent **calcium** ATPases (PMCAs) are enzymatic systems implicated in the extrusion of calcium from the cell. We and others have previously identified molecular interactions between the cytoplasmic COOH-terminal end of PMCA and PDZ domain-containing proteins. These interactions suggested a new role for PMCA as a modulator of signal transduction pathways. The existence of other intracellular regions in the PMCA molecule prompted us to investigate the possible participation of other domains in interactions with different partner proteins. A two-hybrid screen of a human fetal

heart cDNA library, using the region 652-840 of human PMCA4b (located in the catalytic, second intracellular loop) as bait, revealed a novel interaction between PMCA4b and the tumor suppressor RASSF1, a Ras effector protein involved in H-Ras-mediated **apoptosis**. Immunofluorescence co-localization, immunoprecipitation, and glutathione S-transferase pull-down experiments performed in mammalian cells provided further confirmation of the physical interaction between the two proteins. The interaction domain has been narrowed down to region 74-123 of RASSF1C (144-193 in RASSF1A) and 652-748 of human PMCA4b. The functionality of this interaction was demonstrated by the inhibition of the epidermal growth factor-dependent activation of the Erk pathway when PMCA4b and RASSF1 were co-expressed. This inhibition was abolished by blocking PMCA/RASSSF1 association with an excess of a green fluorescent protein fusion protein containing the region 50-123 of RASSF1C. This work describes a novel protein-protein interaction involving a domain of PMCA other than the COOH terminus. It suggests a function for PMCA4b as an organizer of macromolecular protein complexes, where PMCA4b could recruit diverse proteins through interaction with different domains. Furthermore, the functional association with RASSF1 indicates a role for PMCA4b in the modulation of Ras-mediated signaling.

L9 ANSWER 3 OF 48 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:182151 BIOSIS
DOCUMENT NUMBER: PREV200400186069
TITLE: Calmodulin binding to the Fas death domain. Regulation by Fas activation.
AUTHOR(S): Ahn, Eun-Young; Lim, Ssang-Taek; Cook, William J.; McDonald, Jay M. [Reprint Author]
CORPORATE SOURCE: Dept. of Pathology, UAB Center for Metabolic Bone Disease, University of Alabama at Birmingham, 1530 3rd Ave. South, 509 LHRB, Birmingham, AL, 35294-0007, USA mcdonald@path.uab.edu
SOURCE: Journal of Biological Chemistry, (February 13 2004) Vol. 279, No. 7, pp. 5661-5666. print. CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Apr 2004 Last Updated on STN: 7 Apr 2004

AB Fas (APO-1/CD95) is a cell surface receptor that initiates apoptotic pathways, and its cytoplasmic domain interacts with various molecules suggesting that Fas signaling is complex and regulated by multiple proteins. Calmodulin (CaM) is an intracellular Ca2+-binding protein, and it mediates many of the effects of Ca2+. Here, we demonstrate that CaM binds to Fas directly and identify the CaM-binding site on the cytoplasmic death domain (DD) of Fas. Fas binds to CaM-Sepharose and is co-immunoprecipitated with CaM. Other death receptors, such as tumor necrosis factor receptor, DR4, and DR5 do not bind to CaM. The interaction between Fas and CaM is Ca2+-dependent. Deletion mapping analysis with various GST-fused Fas cytoplasmic domain fragments revealed that the fragment containing helices 1, 2, and 3 of the Fas DD has the CaM-binding ability. Sequence analysis of this fragment predicted a potential CaM-binding site in helix 2 and connected loops. A valine 254 to asparagine mutation in this region, which is analogous to the identified mutant allele of Fas in lpr mice that have a deficiency in Fas-mediated **apoptosis**, showed reduced CaM binding. Computer modeling of the interaction between CaM and helix 2 of the Fas DD predicted that amino acids, which are important for Fas-CaM binding, and point mutations of these amino acids caused reduced Fas-CaM binding. The interaction between Fas and CaM is increased apprx2-fold early upon Fas activation (at 30 min) and is decreased to apprx50% of control at 2 h. These findings suggest a novel function of CaM in Fas-mediated **apoptosis**.

L9 ANSWER 4 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:563096 HCAPLUS
DOCUMENT NUMBER: 141:121241
TITLE: Calmodulin-binding domains in Alzheimer's disease proteins: extending the calcium hypothesis

AUTHOR(S): O'Day, Danton H.; Myre, Michael A.
CORPORATE SOURCE: Department of Biology, University of Toronto at Mississauga, Mississauga, ON, L5L IC6, Can.
SOURCE: Biochemical and Biophysical Research Communications (2004), 320(4), 1051-1054
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The calcium hypothesis of Alzheimer's disease (AD) invokes the disruption of calcium signaling as the underlying cause of neuronal dysfunction and ultimately **apoptosis**. As a primary calcium signal transducer, calmodulin (CaM) responds to cytosolic calcium fluxes by binding to and regulating the activity of target CaM-binding proteins (CaMBPs). Ca2+-dependent CaMBPs primarily contain domains (CaMBDs) that can be classified into motifs based upon variations on the basic amphiphilic α-helix domain involving conserved hydrophobic residues at positions 1-10, 1-14 or 1-16. In contrast, an IQ or IQ-like domain often mediates Ca2+-independent CaM-binding. Based on these attributes, a search for CaMBDs reveals that many of the proteins intimately linked to AD may be calmodulin-binding proteins, opening new avenues for research on this devastating disease.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:152821 HCAPLUS
DOCUMENT NUMBER: 140:160866
TITLE: Mitochondrial calcium uptake stimulates nitric oxide production in mitochondria of bovine vascular endothelial cells
AUTHOR(S): Dedkova, Elena N.; Ji, Xiang; Lipsius, Stephen L.; Blatter, Lothar A.
CORPORATE SOURCE: Department of Physiology, Stritch School of Medicine, Loyola University Chicago, Maywood, IL, 60153, USA
SOURCE: American Journal of Physiology (2004), 286(2, Pt. 1), C406-C415
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Although nitric oxide (NO) is a known modulator of cell respiration in vascular endothelium, the presence of a mitochondria-specific nitric oxide synthase (mtNOS) in these cells is still a controversial issue. We have used laser scanning confocal microscopy in combination with the NO-sensitive fluorescent dye DAF-2 to monitor changes in NO production by mitochondria of calf vascular endothelial (CPAE) cells. Cells were loaded with the membrane-permeant NO-sensitive dye 4,5-diaminofluorescein (DAF-2) diacetate and subsequently permeabilized with digitonin to remove cytosolic DAF-2 to allow measurements of NO production in mitochondria ([NO]mt). Stimulation of mitochondrial Ca2+ uptake by exposure to different cytoplasmic Ca2+ concns. (1, 2, and 5 μM) resulted in a dose-dependent increase of NO production by mitochondria. This increase of [NO]mt was sensitive to the NOS antagonist L-N5-(1-iminoethyl)ornithine and the calmodulin antagonist calmidazolium (R-24571), demonstrating the endogenous origin of NO synthesis and its calmodulin dependence. Collapsing the mitochondrial membrane potential with the protonophore FCCP or blocking the mitochondrial Ca2+ uniporter with ruthenium red, as well as blocking the respiratory chain with antimycin A in combination with oligomycin, inhibited mitochondrial NO production Addition of the NO donor spermine NONOate caused a profound increase in DAF-2 fluorescence that was not affected by either of these treatments. The mitochondrial origin of the DAF-2 signals was confirmed by colocalization with the mitochondrial marker MitoTracker Red and by the observation that disruption of caveolae (where cytoplasmic NOS is localized) formation with methyl-β-cyclodextrin did not prevent the increase of DAF-2 fluorescence. The activation of mitochondrial calcium uptake stimulates mtNOS phosphorylation (at Ser-1177) which was prevented by FCCP. The data demonstrate that stimulation of mitochondrial Ca2+ uptake activates NO

production in mitochondria of CPAE cells. This indicates the presence of a mitochondria-specific NOS that can provide a fast local modulatory effect of NO on cell respiration, membrane potential, and **apoptosis**.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:525707 HCAPLUS
DOCUMENT NUMBER: 142:111252
TITLE: Atypical protein-kinase Cζ, but neither conventional Ca2+-dependent protein-kinase C isoenzymes nor Ca2+-calmodulin, participates in regulation of telomerase activity in Burkitt's lymphoma cells
AUTHOR(S): Bakalova, Rumiana; Ohba, Hideki; Zhelev, Zhivko; Kubo, Takanori; Fujii, Masayuki; Ishikawa, Mitsuru; Shinohara, Yasuo; Baba, Yoshinobu
CORPORATE SOURCE: Single-Molecule Bioanalysis Laboratory, National Institute for Advanced Industrial Science and Technology--AIST-Shikoku, Takamatsu, Japan
SOURCE: Cancer Chemotherapy and Pharmacology (2004), 54(2), 161-172
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Purpose: To clarify the role of the pathways dependent on protein-kinase C (PK-C) and Ca2+/calmodulin (CaM) in the regulation of telomerase activity in Burkitt's lymphoma cells. Methods: Burkitt's lymphoma cells (Raji and Daudi) were treated with the PK-C inhibitor, bisindolylmaleimide (BIM), or the CaM inhibitor, trifluoperazine (TFPZ), in a dose-dependent manner and in a time-dependent manner. The activities of PK-C isoenzymes were analyzed fluorimetrically using POLARIS assay kits. CaM-kinase II activity was analyzed radiog., using CaMK-II immunopptn. kinase assay kits. Telomerase activity was detected by a conventional telomeric repeat amplification protocol and Stretch PCR. The level of catalytic subunit of telomerase (hTERT) in drug-treated and nontreated cells was analyzed by flow cytometry using anti-hTERT antibody labeled with ZenonAlexa Fluor-488 IgG. **Apoptosis** was estimated in terms of phosphatidylserine exposure on the cell surface and DNA fragmentation. Results: It was found that BIM inhibited telomerase activity and this process preceded **apoptosis**. The subsequent addition of exogenous PK-C (mixture of isoenzymes) to the cell lyzates restored telomerase activity if incubation of cells with BIM was up to 24 h. Using PK-C isoenzymes, it was established that atypical PK-Cζ, but not conventional Ca2+-dependent PK-Cα, PK-Cβ or PK-Cγ, is responsible for the reactivation of telomerase in BIM-treated cells. BIM also showed a well-expressed cytotoxicity against intact leukemia cells. In contrast, the CaM inhibitor TFPZ showed the same cytotoxic effect without any influence on telomerase activity during incubation for 24 h with leukemia cells. After incubation for 48 h, TFPZ markedly suppressed telomerase activity. However, the effect followed **apoptosis** and appeared to be a result of **cell death**. The addition of exogenous CaMK-II to the cell lyzates obtained from TFPZ-treated cells did not reactivate telomerase. Conclusion: The present study confirmed the participation of atypical PK-Cζ, but not conventional Ca2+-dependent PK-C isoenzymes (α, β, γ) nor the Ca2+/CaM-dependent pathway, in the regulation of telomerase activity in Burkitt's lymphoma cells.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:532418 HCAPLUS
DOCUMENT NUMBER: 141:422678
TITLE: Molecular mechanisms of **apoptosis** in human cholangiocarcinoma: regulation by fas, calcium/calmodulin and interferon-gamma
AUTHOR(S): Ahn, Eun-Young

CORPORATE SOURCE: Univ. of Alabama, Birmingham, AL, USA
SOURCE: (2003) 169 pp. Avail.: UMI, Order No. DA3101501 From: Diss. Abstr. Int., B 2004, 64(8), 3756
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

L9 ANSWER 8 OF 48 NTIS COPYRIGHT 2005 NTIS on STN
ACCESSION NUMBER: 2004(03):00754
NTIS ORDER NUMBER: ADA417425/XAB
TITLE: Exploiting and NQ01-Directed, Calpain-Medicated Apoptotic Pathway for Breast Cancer Therapy. Annual summary rept. 6 Mar 2000-5 Mar 2003.
AUTHOR: Wagner, M. W.; Boothman, D. A.
CORPORATE SOURCE: Case Western Reserve Univ., Cleveland, OH. (004688000 402490)
NUMBER OF REPORT: ADA417425/XAB
92p; Apr 2003
NUMBER OF CONTRACT: DAMD17-00-1-0194
CONTROLLED TERM: Report
COUNTRY: United States
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NTIS Prices: PC A06/MF A01
OTHER SOURCE: GRA&I0403
AB The purpose of this proposal was to further understand the molecular mechanisms of beta-lap-induced **apoptosis**, and its ability to target cancer over normal cells. We believe that beta-lap induces **apoptosis** through changes in intracellular calcium homeostasis and micron-calpain activation. This will be tested via two specific aims using NQ01-expressing and non-expressing (beta-lap sensitive and resistant, respectively) MDA-MB-468 breast cancer cells as a model system. The first aim was to determine changes in intracellular calcium homeostasis before and after beta-lap exposure. Fluorescence calcium dye indicators will be used to determine changes in intracellular calcium levels as well as GFP-**calmodulin calcium** indicators (cameleons, that are targeted to intracellular organelles), for a more accurate determination of where calcium changes are occurring. Analysis of **apoptosis** via flow cytometric analyses will be performed in breast cancer cells in the presence of extracellular calcium chelators, to determine if changes in intracellular calcium concentrations are critical for DNA fragmentation and **cell death**. The second aim will be to determine the role of calpain and its downstream targets in beta-lap-induced **apoptosis**. Calpain activation will be assessed using fluorogenic substrates. Substrate cleavage analyses, in vitro, will be performed using specific downstream targets, as determined from western blot timecourse analyses (PARP, lamin B, and p53). Confocal microscopy with indirect immunofluorescence and Green Fluorescent Protein (OFP)-tagged micron-calpain will be used to examine calpain translocation and co-localization studies with downstream targets.

L9 ANSWER 9 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:146178 HCAPLUS
DOCUMENT NUMBER: 138:379362
TITLE: Calmodulin Mediates Brain-derived Neurotrophic Factor Cell Survival Signaling Upstream of Akt Kinase in Embryonic Neocortical Neurons
AUTHOR(S): Cheng, Aiwu; Wang, Shuqin; Yang, Dongmei; Xiao, Ruiping; Mattson, Mark P.
CORPORATE SOURCE: NIA, Gerontology Research Center, Laboratory of Neurosciences, National Institutes of Health, Baltimore, MD, 21224, USA
SOURCE: Journal of Biological Chemistry (2003), 278(9),

7591-7599
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB As a calcium-sensing protein, calmodulin acts as a transducer of the intracellular calcium signal for a variety of cellular responses. Although calcium is an important regulator of neuronal survival during development of the nervous system and is also implicated in the pathogenesis of neurodegenerative disorders, it is not known if calmodulin mediates these actions of calcium. To determine the role of calmodulin in regulating neuronal survival and death, the authors overexpressed calmodulin with mutations in all four Ca2+-binding sites (CaM(1-4)) or with disabled C-terminal Ca2+-binding sites (CaM(3,4)) in cultured neocortical neurons by adenoviral gene transfer. Long-term neuronal survival was decreased in neurons overexpressing CaM(1-4) and CaM(3,4), which could not be rescued by BDNF. The basal level of Akt kinase activation was decreased, and the ability of BDNF to activate Akt was completely abolished in neurons overexpressing CaM(1-4) or CaM(3,4). In contrast, BDNF-induced activation of p42/44 MAPKs was unaffected by calmodulin mutations. Treatment of neurons with calmodulin antagonists and a phosphatidylinositol 3-kinase inhibitor blocked the ability of BDNF to prevent neuronal death, whereas inhibitors of calcium/calmodulin-dependent protein kinase II did not. The authors' findings demonstrate a pivotal role for calmodulin in survival signaling by BDNF in developing neocortical neurons by activating a transduction pathway involving phosphatidylinositol 3-kinase and Akt. In addition, the authors' findings show that the C-terminal Ca2+-binding sites are critical for calmodulin-mediated cell survival signaling.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:409635 HCAPLUS
DOCUMENT NUMBER: 139:131173
TITLE: From calcium to NF-κB signaling pathways in neurons
AUTHOR(S): Lilienbaum, Alain; Israel, Alain
CORPORATE SOURCE: Unite de Biologie Moleculaire de l'Expression Genique, URA 2582 CNRS, Institut Pasteur, Paris, 75724/15, Fr.
SOURCE: Molecular and Cellular Biology (2003), 23(8), 2680-2698
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB NF-κB plays crucial roles in the nervous system, including potential roles in long-term responses to synaptic plasticity, pro- or antiapoptotic effects during developmental **cell death**, and neurodegenerative disorders. We report here the characterization of signaling pathways leading to the constitutive activation of NF-κB in primary cultures of neonatal cerebellar granule neurons, consecutive to calcium entry into the cytosol. We found that opening of calcium channels at the plasma membrane and at intracellular stores is indispensable for the basal NF-κB activity. We demonstrated further that three cellular sensors of the cytosolic Ca2+ levels, calmodulin, protein kinases C (PKCs), and the p21ras/phosphatidylinositol 3-kinase (PI3K)/Akt pathway are simultaneously involved in the steps linking the Ca2+ second messenger to NF-κB activity. Calmodulin triggers the activity of calcineurin, a phosphatase which plays a role in the basal NF-κB activity, while stimulation of both the calmodulin kinase II and Akt kinase pathways results in the up-regulation of the transcriptional potential of the p65 subunit of NF-κB. Finally, using pharmacol. and mol. approaches, we analyze interactions between these three pathways at different levels and demonstrate a connection between PKCs and PI3K. All three components converge towards NF-κB, at the level of both nuclear translocation and transcriptional activity. These results stand in contrast to the situation in nonneuronal cells, which either do not respond to Ca2+ or do

not simultaneously activate all three cascades. By using a global approach in studying signaling pathways in neurons, these results provide further evidence to validate the concept of networks of transducing cascades, specific to cells and to physiol. situations.
REFERENCE COUNT: 99 THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:658936 HCAPLUS
DOCUMENT NUMBER: 138:236807
TITLE: Participation of the calcium/calmodulin-dependent kinases in hydrogen peroxide-induced IκB phosphorylation in human T lymphocytes
AUTHOR(S): Howe, Christopher J.; LaHair, Michelle M.; Maxwell, Jill A.; Lee, John T.; Robinson, Penni J.; Rodriguez-Mora, Oswaldo; McCubrey, James A.; Franklin, Richard A.
CORPORATE SOURCE: Department of Microbiology and Immunology, Brody School of Medicine, East Carolina University, Greenville, NC, 27858, USA
SOURCE: Journal of Biological Chemistry (2002), 277(34), 30469-30476
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB NF-κB is an important transcription factor that has a role in a variety of responses such as inflammation, oncogenesis, **apoptosis**, and viral replication. Oxidative stress is well known to induce the activation of NF-κB. Cells can be exposed to either endogenously produced oxidants or oxidants produced by surrounding cells. In addition, ischemia reperfusion and certain cancer therapies such as chemotherapy and photodynamic therapy are thought to result in oxygen radical production Because of the important role that NF-κB has in multiple responses, it is critical to determine the mechanisms by which oxidative stress induces NF-κB activity. We report that the calmodulin antagonist W-7 and the calcium/calmodulin-dependent (CaM) kinase inhibitors KN-93 and K252a, can block oxidative stress-induced IκB phosphorylation in Jurkat T lymphocytes. Furthermore, KN-93 but not KN-92 can block hydrogen peroxide-induced Akt and IKK phosphorylation. In addition, we found that expression of a kinase-dead CaM-KIV construct in two cell lines inhibits IκB phosphorylation or degradation and that expression of CaM-KIV augments hydrogen peroxide-induced IκB phosphorylation and degradation Although the CaM kinases appear to be required for this response, increases in intracellular calcium do not appear to be required. These results identify the CaM kinases as potential targets that can be used to minimize NF-κB activation in response to oxidative stress.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:706847 HCAPLUS
DOCUMENT NUMBER: 138:167248
TITLE: Calmodulin overexpression causes Ca2+-dependent **apoptosis** of pancreatic β cells, which can be prevented by inhibition of nitric oxide synthase
AUTHOR(S): Yu, Wei; Niwa, Tae; Miura, Yoshitaka; Horio, Fumihiko; Teradaira, Shin; Ribar, Thomas J.; Means, Anthony R.; Hasegawa, Yoshimi; Senda, Takao; Niki, Ichiro
CORPORATE SOURCE: Dep. Anat., Nagoya Univ. Grad. Sch. Med., Japan
SOURCE: Laboratory Investigation (2002), 82(9), 1229-1239
CODEN: LAINAW; ISSN: 0023-6837
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mechanism of β-cell loss in transgenic mice with elevated levels of β-cell calmodulin (CaM) was investigated. The transgenic mice

experienced a sudden rise in blood glucose levels between 21 and 28 days of age. This change was associated with development of severe hypoinsulinemia and loss of β cells from the islets. Ultrastructural anal. revealed that compromised granule formation and apoptotic changes in the transgenic β cells preceded the onset of hyperglycemia. The i.p. injection of tolbutamide, an antidiabetic sulfonylurea, decreased blood glucose levels but increased the number of apoptotic β cells. Finally, injection of transgenic mice with Nω-nitro-L-arginine Me ester, which inhibits nitric oxide synthase (NOS) activity, prevented hyperglycemia and lessened the changes in number and size of β cells. Because immunofluorescent staining revealed preferential distribution of neuronal NOS (nNOS) in pancreatic β cells, the authors speculate that the overexpression of CaM sensitizes the β cells to Ca2+-dependent activation of nNOS, which mediates **apoptosis**.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 48 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:303948 BIOSIS
DOCUMENT NUMBER: PREV200300303948
TITLE: CALMODULIN MEDIATES BDNF CELL SURVIVAL SIGNALING IN NEOCORTICAL NEURONS.
AUTHOR(S): Cheng, A. [Reprint Author]; Wang, S. [Reprint Author]; Xiao, R. [Reprint Author]; Mattson, M. [Reprint Author]
CORPORATE SOURCE: Dept Neurosci, Gerontology Research Center, Baltimore, MD, USA
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 426.11. http://sfn.scholarone.com. cd-rom.
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 2003
Last Updated on STN: 2 Jul 2003

AB Calcium is an important regulator of neuronal survival and death during development of the nervous system, and is also implicated in the pathogenesis of neurodegenerative disorders.)However, it is not known if calmodulin (CM), a transducer of many responses of cells to calcium, mediates effects of calcium on neuronal survival. We therefore overexpressed Ca2+ insensitive CM with mutations in all four Ca2+ binding sites (CM1-4) and CM with disabled C-terminal Ca2+ binding sites (CM3, 4) in neocortical neurons by adenoviral gene transfer. We found that there is an accelerated neuronal death in both adeno-CM1-4 and adeno-CM3,4 overexpressing neurons, which could not be rescued by the neurotrophic factor BDNF. The basal level of Akt kinase activation was decreased, and the ability of BDNF to activate Akt was completely abolished, in neurons overexpressing CM1-4 or CM3,4 mutants. In contrast, BDNF-induced activation of p42/p44 mitogen activated protein (MAP) kinases was unaffected by either CM1-4 or CM3,4.)Treatment of neurons with CM antagonists and a phosphatidylinositol 3-kinase (PI3K) inhibitor blocked the ability of BDNF to prevent neuronal death, whereas inhibitors of calcium/CM-dependent protein kinase II did not.)Collectively, these findings show that CM plays a pivotal role in survival signaling by BDNF in developing neocortical neurons by activating a transduction pathway involving PI3 kinase and Akt.) In addition, our findings show that the C terminal Ca2+ binding sites are critical for CM-mediated cell survival signaling.

L9 ANSWER 14 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:925544 HCAPLUS
DOCUMENT NUMBER: 136:181246
TITLE: The pro-apoptotic function of death-associated protein kinase is controlled by a unique inhibitory autophosphorylation-based mechanism

AUTHOR(S): Shohat, Galit; Spivak-Kroizman, Taly; Cohen, Ofer; Bialik, Shani; Shani, Gidi; Berrisi, Hanna; Eisenstein, Miriam; Kimchi, Adi
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: Journal of Biological Chemistry (2001), 276(50), 47460-47467
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Death-associated protein kinase is a calcium/calmodulin serine/threonine kinase, which pos. mediates programmed **cell death** in a variety of systems. Here we addressed its mode of regulation and identified a mechanism that restrains its apoptotic function in growing cells and enables its activation during **cell death**. It involves autophosphorylation of Ser308 within the calmodulin (CaM)-regulatory domain, which occurs at basal state, in the absence of Ca2+/CaM, and is inversely correlated with substrate phosphorylation. This type of phosphorylation takes place in growing cells and is strongly reduced upon their exposure to the apoptotic stimulus of C6-ceramide. The substitution of Ser308 to alanine, which mimics the ceramide-induced dephosphorylation at this site, increases Ca2+/CaM-independent substrate phosphorylation as well as binding and overall sensitivity of the kinase to CaM. At the cellular level, it strongly enhances the death-promoting activity of the kinase. Conversely, mutation to aspartic acid reduces the binding of the protein to CaM and abrogates almost completely the death-promoting function of the protein. These results are consistent with a mol. model in which phosphorylation on Ser308 stabilizes a locked conformation of the CaM-regulatory domain within the catalytic cleft and simultaneously also interferes with CaM binding. We propose that this unique mechanism of auto-inhibition evolved to impose a locking device, which keeps death-associated protein kinase silent in healthy cells and ensures its activation only in response to apoptotic signals.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 15 OF 48 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:252247 BIOSIS
DOCUMENT NUMBER: PREV200100252247
TITLE: G protein gamma3 signaling during zebrafish embryonic development.
AUTHOR(S): Kelly, Gregory Mitchell [Reprint author]; Vanderbeld, Barb [Reprint author]; Knowlton, Michelle N. [Reprint author]
CORPORATE SOURCE: Western Science Centre, University of Western Ontario, London, ON, N6A 5B7, Canada
SOURCE: FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A743. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 May 2001
Last Updated on STN: 19 Feb 2002

AB Heterotrimeric guanine nucleotide binding proteins (G proteins) are involved in numerous biological processes where they mediate signal transduction from agonist-bound G protein-coupled receptors (GPCRs) to a variety of intracellular effector molecules and ion channels. G proteins consist of two signaling moieties: a GTP-bound alpha subunit and a betagamma heterodimer. The betagamma dimer is a modulator of G protein-mediated cellular responses, and a major determinant of signaling fidelity between GPCRs and downstream effectors. We have isolated a cDNA that encodes a zebrafish G protein gamma subunit. BLAST search analysis revealed that the zebrafish gamma subunit is 93% identical and 97% similar

to mammalian gamma3 proteins. gamma3 transcripts are first detected at the 14-somite stage and are expressed preferentially in the trigeminal ganglia, the forebrain, ventrolateral regions of the mid- and hindbrain, and in the spinal cord. The zebrafish gamma3 subunit forms a heterodimer with a mammalian beta subunit and as a complex, binds to **calmodulin** in a **calcium**-dependent manner. Overexpression of a beta2gamma3 complex in zebrafish embryos leads to the loss of dorsoanterior structures and expansion of ventral structures, possibly owing to an up-regulation of mitogen-activated protein kinase activity and/or a decline in protein kinase A signaling. Attempts to down-regulate gamma3 activity using double-stranded RNA interference were unsuccessful, but blocking translation of the protein using an antisense gamma3 morpholino oligomer induces **apoptosis** in cells that express gamma3 and in neighbouring non-gamma3-expressing cells. Together, these data indicate that a betagamma3 heterodimer plays a role in signal transduction events that occur in specific regions of the developing zebrafish nervous system and that correct betagamma3 signaling is required to prevent gamma3-expressing neural cells from becoming apoptotic.

L9 ANSWER 16 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:520534 HCAPLUS
DOCUMENT NUMBER: 135:352724
TITLE: Ca2+-calmodulin antagonist chlorpromazine and poly(ADP-ribose) polymerase modulators 4-aminobenzamide and nicotinamide influence hepatic expression of BCL-XL and P53 and protect against acetaminophen-induced programmed and unprogrammed **cell death** in mice
AUTHOR(S): Ray, S. D.; Balasubramanian, G.; Bagchi, D.; Reddy, C. S.
CORPORATE SOURCE: Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Department of Pharmacology, Toxicology and Medicinal Chemistry, Molecular Toxicology Program, Long Island University, Brooklyn, NY, USA
SOURCE: Free Radical Biology & Medicine (2001), 31(3), 277-291
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acetaminophen (AAP), the analgesic hepatotoxicant, is a powerful inducer of oxidative stress, DNA fragmentation, and **apoptosis**. The anti-apoptotic oncogene bcl-XL, and the pro-apoptotic oncogene p53 are two key regulators of cell cycle progression and/or **apoptosis** subsequent to DNA damage in vitro and in vivo. This study investigated the effect of AAP on the expression of these oncogenes and whether agents that modulate DNA fragmentation (chlorpromazine, CPZ) and DNA repair through poly(ADP-Ribose) polymerase (PARP) activity (4-AB: 4-aminobenzamide) can protect against AAP-induced hepatotoxicity by inhibiting oxidative stress, DNA fragmentation, and/or by altering the expression of bcl-XL and p53. In addition, the protective effect of supplemental nicotinamide (NICO), known to be depleted in cells with high PARP activity during DNA repair, is similarly evaluated. Male ICR mice (3 mo old) were administered vehicle alone; nontoxic doses of 4-AB (400 mg/kg, i.p.), NICO (250 mg/kg, i.p.) or CPZ (25 mg/kg, i.p.), hepatotoxic dose of AAP alone (500 mg/kg, i.p.), or AAP plus one of the protective agents 1 h later. All animals were sacrificed 24 h following AAP administration. Serum alanine aminotransferase activity (ALT), hepatic histopathol. and lipid peroxidn., DNA damage, and expression of bcl-XL and p53 (western blot anal.) were compared in various groups. All of the three agents significantly prevented AAP-induced liver injury, lipid peroxidn., DNA damage, and associated apoptotic and necrotic **cell deaths**, 4-AB being the most effective and NICO the least. Compared to control, there was a considerable decrease in bcl-XL expression, and an increase in p53 expression in AAP-exposed livers. The effect of AAP on bcl-XL was antagonized and that on p53 was synergized by the PARP-modulator 4-AB as well as NICO, whereas the endonuclease inhibitor CPZ was without effect on either bcl-XL or p53 expression. These results suggest that the hepatotoxic effect of AAP involves multiple

mechanisms including oxidative stress, upregulation of endonuclease (or caspase-activated DNAse) and alteration of pro- and anti-apoptotic oncogenes. The observed antagonism of AAP-induced hepatocellular **apoptosis** and/or necrosis by modulators of multiple processes including DNA repair suggests the likelihood that a more effective therapy against AAP intoxication should involve a combination of antidotes.
REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 17 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:588638 HCAPLUS
DOCUMENT NUMBER: 135:339479
TITLE: Preliminary study on signal transduction in murine thymocyte **apoptosis** induced by 17β-estradiol
AUTHOR(S): Wang, Yu; Wang, Wei; Wen, Jie; Wang, Chaomei; Hu, Jiancheng; Zheng, Haijin
CORPORATE SOURCE: School of Life Sciences, Lanzhou University, Lanzhou, 730000, Peop. Rep. China
SOURCE: Lanzhou Daxue Xuebao, Ziran Kexueban (2001), 37(3), 92-96
CODEN: LCTHAF; ISSN: 0455-2059
PUBLISHER: Lanzhou Daxue
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB The relationship between murine thymocyte **apoptosis** induced by 17β-estradiol and second signal elements Ca2+/CaM was studied. Thymocyte **apoptosis** was induced by 17β-estradiol, but repressed when extracellular Ca2+ was chelated by EGTA. The intracellular free Ca2+ concentration was rapidly increased by 17β-estradiol. CaM content in thymocytes was remarkably decreased by 17β-estradiol. The results showed that the signal transduction pathway of Ca2+/CaM might play a part in murine thymocyte **apoptosis** induced by 17β-estradiol.

L9 ANSWER 18 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:499586 HCAPLUS
DOCUMENT NUMBER: 138:13381
TITLE: Analysis of calcium-induced **apoptosis** in HIV-1 gp 160-expressing cells
AUTHOR(S): Sasaki, Masafumi; Yoshida, Hiroki
CORPORATE SOURCE: Medical Institute of Bioregulation, Kyushu University, Fukuoka, 812-8582, Japan
SOURCE: Seirigaku Gijutsu Kenkyukai Hokoku (2001), 23, 51-54
CODEN: SGKHEB; ISSN: 0285-3299
PUBLISHER: Okazaki Kokuritsu Kyodo Kenkyu Kiko, Seirigaku Kenkyusho Gijutsuka
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB HIV-1 infection leads to acquired immunodeficiency syndrome(AIDS), characterized by loss of CD4 +T cells in the immune system, the authors demonstrated that the induced expression of HIV-1 gp160 in CD4+ cells lead to **apoptosis**. the authors also reported that this **apoptosis** was preceded by the intracellular calcium concentration induced by the interaction of gp160 with calmodulin. Sustained increases in intracellular calcium ion lead to activation of calcineurin, which in turn, dephosphorylated BAD, interferes with Bcl-xL thereby disturbing function of mitochondria. Cytochrome c is the thus released from damaged disturbed mitochondria in to cytoplasm resulting in the activation of Apafl-caspase9-Caspase3 cascade. In addition to the involvement of mitochondria in apoptotic pathways. In response to "ER stress" including disruption of ER calcium homeostasis and accumulation of excess of proteins in ER, while caspase 12 is localized to ER and activated leading to **apoptosis** death of cells.

L9 ANSWER 19 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:523331 HCAPLUS
DOCUMENT NUMBER: 134:1258
TITLE: Calcium regulates transcriptional repression of myocyte enhancer factor 2 by histone deacetylase 4

AUTHOR(S): Youn, Hong-Duk; Grozinger, Christina M.; Liu, Jun O.
CORPORATE SOURCE: Center for Cancer Research, Department of Chemistry and Biology, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
SOURCE: Journal of Biological Chemistry (2000), 275(29), 22563-22567
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The myocyte enhancer factor 2 (MEF2) consists of a family of transcription factors that play important roles in a number of physiol. processes from muscle cell differentiation to neuronal survival and T cell **apoptosis**. MEF2 has been reported to be associated with several distinct repressors including Cabin1(cain), MEF2-interacting transcriptional repressor (MITR), and HDAC4. It has been previously shown that Cabin1 is associated with MEF2 in a calcium-sensitive manner; activated calmodulin binds to Cabin1 and releases it from MEF2. However, it was not known whether the binding of HDAC4 and MITR to MEF2 is also regulated by calcium. We report that HDAC4 and MITR contain calmodulin-binding domains that overlap with their MEF2-binding domains. Binding of calmodulin to HDAC4 leads to its dissociation from MEF2, relieving MEF2 from the transcriptional repression by HDAC4. Together, HDAC4, MITR, and Cabin1 constitute a family of calcium-sensitive transcriptional repressors of MEF2.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 20 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:642873 HCAPLUS
DOCUMENT NUMBER: 133:360428
TITLE: Activation of calcium/calmodulin regulated kinases
AUTHOR(S): Wilmanns, Matthias; Gautel, Mathias; Mayans, Olga
CORPORATE SOURCE: EMBL DESY, Hamburg, D-22603, Germany
SOURCE: Cellular and Molecular Biology (Paris) (2000), 46(5), 883-894
CODEN: CMOBEF; ISSN: 0145-5680
PUBLISHER: C.M.B. Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Among numerous protein kinases found in mammalian cell systems there is a distinct subfamily of serine/threonine kinases that are regulated by calmodulin or other related activators in a calcium concentration dependent manner. Members of this family are involved in various cellular processes like cell proliferation and **death**, **cell** motility and metabolic pathways. In this contribution we shall review the available structural biol. data on five members of this kinase family (calcium/calmodulin dependent kinase, twitchin kinase, titin kinase, phosphorylase kinase, myosin light chain kinase). As a common element, all these kinases contain a regulatory tail, which is C-terminal to their catalytic domain. The available 3D structures of two members, the serine/threonine kinases of the giant muscle proteins twitchin and titin in the autoinhibited conformation, show how this regulatory tail blocks their active sites. The structures suggest that activation of these kinases requires unblocking the active site from the C-terminal extension and conformational rearrangement of the active site loops. Small angle scattering data for myosin light chain kinase indicate a complete release of the C-terminal extension upon calcium/calmodulin binding. In addition, members of this family are regulated by diverse add-on mechanisms, including phosphorylation of residues within the activation segment or the P+1 loop as well as by addnl. regulatory subunits. The available structural data lead to the hypothesis of two different activation mechanisms upon binding to calcium sensitive proteins. In one model, the regulatory tail is entirely released ("fall-apart"). The alternative model ("looping-out") proposes a two-anchored release mechanism.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 21 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:645122 HCAPLUS
DOCUMENT NUMBER: 134:275582
TITLE: Ca2+ mobilization induced by W-7 in MG63 human osteosarcoma cells
AUTHOR(S): Jan, Chung-Ren; Lu, Cheng-Hsien; Chen, Yu-Chih; Cheng, Jin-Shiung; Tseng, Li-Ling; Wang, Jun-Wen
CORPORATE SOURCE: Department of Medical Education and Research, Taiwan and Department of Biology and Institute of Life Sciences, Kaohsiung Veterans General Hospital, National Sun Yat-sen University, Kaohsiung, Taiwan
SOURCE: Pharmacological Research (2000), 42(4), 323-327
CODEN: PHMREP; ISSN: 1043-6618
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide hydrochloride (W-7), a widely used calmodulin inhibitor, on intracellular free Ca2+ levels ([Ca2+]i) in MG63 human osteosarcoma cells was explored using fura-2 as a Ca2+probe. W-7 (20-1000 μM) induced an increase in [Ca2+]iin a dose-dependent manner, with an EC50of 100 μM. The [Ca2+]i signal comprised an initial rise and a sustained plateau without decay within 5 min. External Ca2+ removal decreased the Ca2+ signals by reducing the peak and sustained phase, indicating W-7-activated intracellular Ca2+ release and extracellular Ca2+ influx. W-7 (500 μM) failed to induce a [Ca2+]i increase in a Ca2+-free medium after pre-treatment with thapsigargin (1 μM), an endoplasmic reticulum Ca2+ pump inhibitor. Conversely, W-7 pre-treatment abolished the Ca2+ release induced by thapsigargin. This suggests that W-7 (500 μM) released internal Ca2+ mainly from the endoplasmic reticulum. The addition of 3 mM Ca2+ increased [Ca2+]i dose-dependently after preincubation with 20-1000 μM W-7 in a Ca2+-free medium, implying that W-7 induced capacitative Ca2+ entry. W-7-induced Ca2+ release was not altered by inhibiting phospholipase C with 2 μM 1-(6-((17 β - 3-methoxyestra-1,3,5(10)-trien-17-yl)amino)hexyl)-1H-pyrrole-2,5-dione (U73122). Tryphan blue assay demonstrated that W-7 (200 μM) caused gradual **cell death** within 30 min of the initial drug exposure. Together, it was found that W-7 induced [Ca2+]i increases in human osteosarcoma cells by releasing internal Ca2+ from the endoplasmic reticulum, and also by triggering Ca2+ influx. W-7 may be cytotoxic to osteosarcoma cells. (c) 2000 The Italian Pharmacological Society.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 22 OF 48 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:25940 BIOSIS
DOCUMENT NUMBER: PREV200100025940
TITLE: Biology of multiple drug resistance in acute leukemia.
AUTHOR(S): Norgaard, Jan Maxwell [Reprint author]; Hokland, Peter
CORPORATE SOURCE: Haematologisk Afd., Aarhus Amtssygehus, Tage-Hansens Gade 2, DK-8000, Aarhus C, Denmark
janmaxgaard@dadlnet.dk
SOURCE: International Journal of Hematology, (October, 2000) Vol. 72, No. 3, pp. 290-297. print.
ISSN: 0925-5710.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jan 2001
Last Updated on STN: 12 Feb 2002
AB Since the early 1970s, multiple drug resistance (MDR) has been known to exist in cancer cells and is thought to be attributable to a membrane-bound, energy-dependent pump protein (P-glycoprotein (P-gp)) capable of extruding various related and unrelated chemotherapeutic drugs. P-gp is coded for by the MDR1 gene, which in the human genome is located on the long arm of chromosome 7 (7q21-31). At the cellular level, the function of P-gp has been extensively investigated in human cancer. Although innumerable reports have been published in which P-gp has been

shown to confer MDR to malignant (including leukemia) cells, so far, large-scale studies in the clinical setting have not convincingly proven that MDR1 plays a major role in clinical drug resistance when the influence of other known prognostic factors in human leukemia are taken into account. At present, results from phase 3 clinical trials evaluating the efficiency of inhibiting (or reversing) the function of P-gp in hematologic malignancies are eagerly awaited. Moreover, the horizon of cellular drug resistance in human cancer has during recent years widened dramatically. Thus, an array of different molecules and mechanisms by which resistant cells can escape the cytotoxic effect of anticancer drugs has now been identified. These molecules and mechanisms include **apoptosis**-related proteins. In this article, we review the different methods for determining MDR and, in particular, methods for determining P-gp/MDR1, with special reference to their potential importance for therapeutic strategies in human acute leukemia.

L9 ANSWER 23 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:696159 HCAPLUS
DOCUMENT NUMBER: 132:320083
TITLE: Calcium, **calmodulin**, and **calcium** /calmodulin-dependent kinase and phosphatase: roles in neuronal **cell death**
AUTHOR(S): McGinnis, Kim Melinda
CORPORATE SOURCE: Univ. of Michigan, Ann Arbor, MI, USA
SOURCE: (1999) 275 pp. Avail.: UMI, Order No. DA9929894 From: Diss. Abstr. Int., B 1999, 60(5), 2077
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

L9 ANSWER 24 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:811348 HCAPLUS
DOCUMENT NUMBER: 132:46958
TITLE: Cloning, sequence and therapeutic applications of **cell death**-promoting DAP-kinase related protein kinase DRP-1 and
INVENTOR(S): Kimchi, Adi
PATENT ASSIGNEE(S): Yeda Research and Development Company Ltd., Israel; McInnis, Patricia A.
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966030	A1	19991223	WO 1999-US13411	19990615
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9944408	A1	20000105	AU 1999-44408	19990615
GB 2354522	A1	20010328	GB 2001-660	19990615
GB 2354522	B2	20040121		

PRIORITY APPLN. INFO.: US 1998-89294P P 19980615
WO 1999-US13411 W 19990615

AB A new protein kinase, DAP-Kinase related 1 protein (DRP-1), which is a novel homolog of DAP-kinase, has been isolated. and cDNA sequence and amino acid sequences of human DRP-1 are reported. This novel calmodulin-dependent kinase is a **cell death**-promoting protein functioning in the biochem. pathway which involves DAP (death-associated protein)-kinase (e.g., forming a cascade of sequential

kinases, one directly activating the other). Alternatively, the two kinases may operate to promote **cell death** in parallel pathways.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 25 OF 48 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 1999374642 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10446976
TITLE: Idoxifene antagonizes estradiol-dependent MCF-7 breast cancer xenograft growth through sustained induction of **apoptosis**.
AUTHOR: Johnston S R; Boeddinghaus I M; Riddler S; Haynes B P; Hardcastle I R; Rowlands M; Grimshaw R; Jarman M; Dowsett M
CORPORATE SOURCE: Department of Medicine, The Royal Marsden NHS Trust, London, England.. stephen@icr.ac.uk
SOURCE: Cancer research, (1999 Aug 1) 59 (15) 3646-51. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990921
Last Updated on STN: 19990921
Entered Medline: 19990907

AB Idoxifene is a novel selective estrogen (E2) receptor (ER) modulator that is currently in clinical development for the treatment of breast cancer. Compared to tamoxifen, idoxifene is metabolically more stable, with a higher relative binding affinity for the ER and reduced agonist activity on breast and uterine cells. Idoxifene also inhibits **calmodulin**, a **calcium**-binding protein that is involved in cell signal transduction pathways. In this study, the abilities of idoxifene and tamoxifen to antagonize E2-dependent MCF-7 xenograft growth in oophorectomized athymic mice were compared. The basis for idoxifene's antitumor activity was examined by comparing the effectiveness of the clinically used transisomer (referred to here as idoxifene) with its cis-isomer, which has a 50-fold lower relative binding affinity for ER than idoxifene but similar calmodulin-inhibitory activity. Changes in tumor cell proliferation, **apoptosis**, and ER-dependent protein expression were studied. Both idoxifene and tamoxifen significantly inhibited E2-dependent tumor growth, whereas cis-idoxifene had little effect. Withdrawal of E2 support induced significant tumor regression due to impaired cell proliferation (Ki-67 score, 9 versus 51% compared to E2 controls) and induction of **apoptosis** (3.6 versus 0.9% compared to E2 controls). Both anti-E2s inhibited cell proliferation and caused a significant 3-fold induction of **apoptosis** in E2 supported tumors after 1 week, which was maintained for 3 months with idoxifene (3.1 versus 0.48% compared to E2 controls) but decreased back to baseline in tumors treated with tamoxifen (0.69%). In contrast, cis-idoxifene had no effect on either cell proliferation or **apoptosis**. Both tamoxifen and idoxifene initially induced ER expression, whereas prolonged therapy with tamoxifen significantly reduced progesterone receptor levels. In conclusion, idoxifene resulted in similar inhibition of E2-dependent MCF-7 xenograft growth compared with tamoxifen, an effect that is mediated via ER rather than through calmodulin. Sustained induction of **apoptosis** may contribute to prolonged antagonism of E2-dependent growth, and it occurred to a greater extent following 3 months of idoxifene, compared to tamoxifen.

L9 ANSWER 26 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:735893 HCAPLUS
DOCUMENT NUMBER: 132:48198
TITLE: Chlorpromazine inhibits hepatocyte **apoptosis** caused by withdrawal of phenobarbital in mice
AUTHOR(S): He, Ping; Yan, Zhen-Lin; Wu, Meng-Chao; Li, Lin-Fang; Guo, Ya-Jun
CORPORATE SOURCE: Eastern Institute of Hepatobiliary Surgery, Second Military Medical University, Shanghai, 200438, Peop.

Rep. China
SOURCE: Zhongguo Yaoli Xuebao (1999), 20(11), 970-974
CODEN: CYLPDN; ISSN: 0253-9756
PUBLISHER: Kexue Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The inhibitory effects of chlorpromazine (Chl), verapamil, and aspirin on hepatocyte **apoptosis** induced by the cessation of phenobarbital (Phe) treatment were studied in mice. Liver DNA content, ratio of liver weight/body weight, DNA fragmentation, DNA electrophoresis, the end-labeling test (TUNEL), and the morphol. changes of liver cells as indexes of liver mass and hepatocyte **apoptosis** were applied to investigate (1) the kinetic process of hepatocyte proliferation induced by Phe 75 mg·kg-1 i.p. and the regression of hyperplastic liver caused by withdrawal of Phe in mice, (2) the effect of Chl 25 mg·kg-1, verapamil 50 mg·kg-1 or aspirin 60 mg·kg-1 i.p. on mouse hepatocyte **apoptosis**, and (3) the time course of effects of Chl on the regression of liver size and DNA fragmentation content after withdrawal of Phe. The process of hepatocyte proliferation and regression induced by administration and withdrawal of Phe in mice consisted of 4 phases: proliferation, plateau, rapid regression, and slow regression phases. In the rapid regression phase, the typic changes of hepatocyte **apoptosis** were found, which was prevented in early period by the Ca2+-calmodulin antagonist Chl, but not by verapamil or aspirin. CONCLUSION: The Ca2+-calmodulin played an important role in the hepatocyte **apoptosis** caused by withdrawal of Phe.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 27 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:504383 HCAPLUS
DOCUMENT NUMBER: 131:295206
TITLE: Effects of Ca2+-Ionophore A23187 and Calmodulin Antagonists on Regulatory Mechanisms of Glycolysis and Cell Viability of NIH-3T3 Fibroblasts
AUTHOR(S): Ashkenazy-Shahar, Michal; Beitner, Rivka
CORPORATE SOURCE: Health Sciences Research Center, Faculty of Life Sciences, Bar-Ilan University, Ramat Gan, 52900, Israel
SOURCE: Molecular Genetics and Metabolism (1999), 67(4), 334-342
CODEN: MGMEFF; ISSN: 1096-7192
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We studied here, in NIH-3T3 fibroblasts, the effect of the Ca2+-ionophore A23187 (which is known to increase intracellular-free Ca2+) on the control of glycolysis and cell viability and the action of calmodulin antagonists. Time-response studies with Ca2+-ionophore A23187 have revealed dual effects on the distribution of phosphofructokinase (PFK) (EC 2.7.1.11), the rate-limiting enzyme of glycolysis, between the cytoskeletal and cytosolic (soluble) fractions of the cell. A short incubation (maximal effect after 7 min) caused an increase in cytoskeleton-bound PFK with a corresponding decrease in soluble activity. This leads to an enhancement of cytoskeletal glycolysis. A longer incubation with Ca2+-ionophore caused a reduction in both cytoskeletal and cytosolic PFK and **cell death**. Both the "physiol." and "pathol." phases of the Ca2+-induced changes in the distribution of PFK were prevented by treatment with three structurally different calmodulin antagonists, thioridazine, an antipsychotic phenothiazine, clotrimazole, from the group of antifungal azole derivs. that were recently recognized as calmodulin antagonists, and CGS 9343B, a more selective inhibitor of calmodulin activity. The longer incubation with Ca2+-ionophore also induced a decrease in the levels of glucose 1,6-bisphosphate and fructose 1,6-bisphosphate, the two allosteric stimulatory signal mols. of glycolysis. All these pathol. changes preceded the reduction in cell viability, and a strong correlation was found between the fall in ATP and **cell death**. All three calmodulin antagonists prevented the pathol. reduction in the levels of the allosteric effectors, ATP and cell

viability. These expts. may throw light on the mechanisms underlying the therapeutic action of calmodulin antagonists that we previously found in treatment of the proliferating melanoma cells, on the one hand, and skin injuries, on the other hand. (c) 1999 Academic Press.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 28 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:247003 HCAPLUS
DOCUMENT NUMBER: 131:71783
TITLE: Effects of calmodulin antagonists and intracellular calcium concentration on viability of human decidual cells in vitro
AUTHOR(S): Xie, Xiaoying; Yang, Renshu; Mao, Weiping
CORPORATE SOURCE: Department of Biology, Nanjing Normal University, Nanjing, 210097, Peop. Rep. China
SOURCE: Dongwu Xuebao (1999), 45(1), 80-87
CODEN: TWHPA3; ISSN: 0001-7302
PUBLISHER: Kexue Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The effects of 2 specific calmodulin (CaM) antagonists, trifluoperazine (TFP) and dauricine derivs. (Dd3), as well as EGTA and A23187 on the viability of human decidual cells in vitro were studied. TFP, Dd3, and EGTA inhibited the viability of decidual cells in a dose-and/or time-related manner. The higher concentration and the longer time the cells were incubated with the agents, the more significant the inhibition became. TFP (≥15 μmol L-1), Dd3 (≥25 μmol·L-1) or EGTA (2 mmol·L-1) significantly inhibited the viability of decidual cells. TFP and Dd3 decreased the cell viability to 8.7% and 12.0% of the control, resp. after 96 h of culture. EGTA decreased the cell viability to 28.6% of the control after 72 h. A23187 (6 μmol·L-1) stimulated the cell viability to a certain extent, but the stimulatory effect decreased with time. The presence of EGTA obviously enhanced the inhibition of TFP on the viability of the decidual cells. The results show that Ca2+-CaM system might be directly involved in the development and maintenance of uterine decidua and play an important role. This might be one of the main mechanisms of anti-fertility action of CaM antagonists.

L9 ANSWER 29 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:629232 HCAPLUS
DOCUMENT NUMBER: 130:64418
TITLE: **Apoptosis** of leukemic lymphocytes mediated by purinergic P2z receptors
AUTHOR(S): Peng, Liming; Bradely, C. J.; Wiley, J. S.
CORPORATE SOURCE: Department of Laboratory Medicine, School of Medicine, West China University of Medical Sciences, Chengdu, 610041, Peop. Rep. China
SOURCE: Zhonghua Yixue Zazhi (1998), 78(7), 508-511
CODEN: CHHTAT; ISSN: 0376-2491
PUBLISHER: Zhonghua Yixue Zazhi
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The role of purinergic P2z receptors for **apoptosis** of human leukemic lymphocytes induced by extracellular ATP (ATP) was studied. A total of 11 B-CLL patients were studied with regard to exposure of leukemic lymphocytes with (n = 8) or without (n = 3) P2z receptors to ATP, benzoylbenzoic-ATP (BzATP), 2-methylthio-ATP , adenosine-5'-[γ-thio] triphosphate (ATP-γS), and other nucleosides for 8 h in vitro. **Apoptosis** was detected by electron microscopy (EM), agarose gel electrophoresis, and quant. assay-TdT assay. **Apoptosis** was detected only in leukemic lymphocytes with P2z receptors. ATP-induced DNA strand breaks occurred specifically with BzATP, ATP and 2MeSATP, but not for analog ATP-γS nor other nucleosides by using a quant. assay. ATP-induced DNA fragmentation was fully blocked by pretreatment with oxidized ATP (OxATP), a compound recently shown to block P2z receptors. The Ca2+/calmodulin complex played a role in the regulation of the **apoptosis** induced by ATP on CLL cells, because an antagonist of this complex, 1-[N,O-bis(5-isoquinolinesulfonyl)-N- methyl-L-tyrosyl]-4-

phenylpiperazine (KN-62) was found to inhibit the ATP-induced **apoptosis**. These data show that P2z receptors on lymphocytes play an important role in **apoptosis** induced by ATP in vitro.

L9 ANSWER 30 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:463563 HCAPLUS
DOCUMENT NUMBER: 129:185261
TITLE: Sulfur mustard induces markers of terminal differentiation and **apoptosis** in keratinocytes via a Ca2+-calmodulin and caspase-dependent pathway
AUTHOR(S): Rosenthal, Dean S.; Simbulan-Rosenthal, Cynthia M. G.; Iyer, Sudha; Spoonde, Alexander; Smith, William; Ray, Radharaman; Smulson, Mark E.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Georgetown University School of Medicine, Washington, DC, 20007, USA
SOURCE: Journal of Investigative Dermatology (1998), 111(1), 64-71
CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sulfur mustard (SM) induces vesication via poorly understood pathways. The blisters that are formed result primarily from the detachment of the epidermis from the dermis at the level of the basement membrane. In addition, there is toxicity to the basal cells, although no careful study has been performed to determine the precise mode of **cell death** biochem. We describe here two potential mechanisms by which SM causes basal **cell death** and detachment: namely, induction of terminal differentiation and **apoptosis**. In the presence of 100 μM SM, terminal differentiation was rapidly induced in primary human keratinocytes that included the expression of the differentiation-specific markers K1 and K10 and the crosslinking of the cornified envelope precursor protein involucrin. The expression of the attachment protein, fibronectin, was also reduced in a time- and dose-dependent fashion. Features common to both differentiation and **apoptosis** were also induced in 100 μM SM, including the rapid induction of p53 and the reduction of Bcl-2. At higher concns. of SM (i.e., 300 μM), formation of the characteristic nucleosome-sized DNA ladders, TUNEL-pos. staining of cells, activation of the cysteine protease caspase-3/apopain, and cleavage of the death substrate poly(ADP-ribose) polymerase, were observed both in vivo and in vitro. Both the differentiation and the apoptotic processes appeared to be calmodulin dependent, because the calmodulin inhibitor W-7 blocked the expression of the differentiation-specific markers, as well as the apoptotic response, in a concentration-dependent fashion. In addition, the intracellular Ca2+ chelator, BAPTA-AM, blocked the differentiation response and attenuated the apoptotic response. These results suggest a strategy for designing inhibitors of SM vesication via the Ca2+-calmodulin or caspase-3/PARP pathway.
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 31 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:786830 HCAPLUS
DOCUMENT NUMBER: 128:111942
TITLE: Calcium signaling in the cell nucleus. [Erratum to document cited in CA128:58603]
AUTHOR(S): Santella, L.; Carafoli, E.
CORPORATE SOURCE: Stazione Zoologica "A. Dohrn", Naples, I-80121, Italy
SOURCE: FASEB Journal (1997), 11(14), 1330
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB The Nov. cover illustration and Fig. 2 are modified from Shibasaki, R., Price, E. R., Milan, D., and McKeon, F. (1996) Role of kinases and the phosphatase calcineurin in the nuclear shuttling of transcription factor

NF-AT4. Nature (London) 382, 370-373.

L9 ANSWER 32 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:728193 HCAPLUS
DOCUMENT NUMBER: 128:58603
TITLE: Calcium signaling in the cell nucleus
AUTHOR(S): Santella, Luigia; Carafoli, Ernesto
CORPORATE SOURCE: Stazione Zoologica "A. Dohrn", Naples, I-80121, Italy
SOURCE: FASEB Journal (1997), 11(13), 1091-1109
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 250 refs. Regulation of Ca2+ in the nucleus is a debated issue, essentially due to the presence in the envelope of the pores, which are large enough to permit the passive traffic of small mols. like Ca2+. Work with a number of cell systems has shown that Ca2+ diffuses freely in and out of the nucleus, whereas other studies have suggested instead that the nuclear envelope could become an efficient Ca2+ filter:electrophysiol. work has shown that it could become impermeable to ions, and persistent nucleus cytoplasmic Ca2+ gradients have been documented in various cell types. The problem of the control of nuclear Ca2+ thus is still open: mechanisms for gating of the pores, based on the state of depletion of the cell Ca2+ stores, have been proposed. Irresp. of the mechanisms for possible pore gating, a final picture on the traffic of Ca2+ in and out of the nucleus must also include the Ca2+ pump as well as the InsP3 and cyclic ADP ribose-modulated Ca2+ channels in the envelope. The channels can be activated by their ligands from inside the nucleus, producing Ca2+ transients in the nucleoplasm; the machinery for producing InsP3 has been documented in the envelope. Most Ca2+-sensitive nuclear functions are jointly modulated by Ca2+ and calmodulin: calmodulin-dependent kinases and the calmodulin-dependent phosphatase calcineurin have been documented in the nucleus. An interesting case for the modulation of intranuclear processes by calmodulin-dependent kinases is that of immediate early genes, i.e., CREB. Other Ca2+-modulated nuclear processes are calmodulin independent: chief among them is the intranucleosomal cleavage of chromatin and the fragmentation of nuclear proteins during **apoptosis**.
REFERENCE COUNT: 250 THERE ARE 250 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 33 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:106767 HCAPLUS
DOCUMENT NUMBER: 126:128057
TITLE: Interaction between calcium ions and Bacillus thuringiensis toxin activity against Sf9 cells (Spodoptera frugiperda, Lepidoptera)
AUTHOR(S): Monette, R.; Potvin, L.; Baines, D.; Laprade, R.; Schwartz, J. L.
CORPORATE SOURCE: Biotechnology Research Institute, National Research Council, Montreal, QC, Can.
SOURCE: Applied and Environmental Microbiology (1997), 63(2), 440-447
CODEN: AEMIDF; ISSN: 0099-2240
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of calcium ions and modulators of calcium movement on Bacillus thuringiensis insecticidal protein toxicity were investigated with Sf9 cells (Spodoptera frugiperda, fall armyworm) by a new B. thuringiensis toxicity assay based on measurement of fluorescence of ethidium homodimer, a high-affinity DNA stain. CryIC toxicity was substantially stimulated by extracellular calcium in a dose-dependent way (in the millimolar range), while toxicity enhancement could not be replicated when calcium was replaced by barium. This incremental toxicity was reduced by cobalt and lanthanum ions, two inorg.-calcium transport inhibitors. Methoxyverapamil, a voltage-dependent calcium channel blocker, and

nifedipine, an inhibitor of dihydropyridine-sensitive L-type calcium channels, had no effect on CryIC toxin activity, but BAY K 8644, an L-type calcium channel activator, increased CryIC activity at high concns. of extracellular calcium. While A23187, a calcium ionophore, and TMB-8, an inhibitor of intracellular-calcium mobilization, did not change CryIC-induced mortality, thapsigargin, an inhibitor of calcium uptake in intracellular stores, and more particularly trifluoperazine, which inhibits calcium-calmodulin-dependent processes, increased CryIC-mediated toxicity. The incremental effect of extracellular calcium on CryIC-induced toxicity was consistent with an increased concentration of intracellular calcium.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 34 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:296270 HCAPLUS

DOCUMENT NUMBER: 127:758

TITLE: Protection against methoxyacetic acid-induced spermatocyte **apoptosis** with calcium channel blockers in cultured rat seminiferous tubules: possible mechanisms

AUTHOR(S): Li, Ling-Hong; Wine, Robert N.; Miller, David S.; Reece, Jeffrey M.; Smith, Marjo; Chapin, Robert E.

CORPORATE SOURCE: Reproductive Toxicology Group, National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC, 27709, USA

SOURCE: Toxicology and Applied Pharmacology (1997), 144(1), 105-119
CODEN: TXAPA9; ISSN: 0041-008X

PUBLISHER: Academic

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A calcium-mediated mechanism underlying spermatocyte **apoptosis** induced by 2-methoxyethanol (2-ME) has been previously proposed. This hypothesis was tested in vitro in the present study using cultured juvenile (25 days old) and adult rat seminiferous tubules (JRST and ARST, resp.) with methoxyacetic acid (MAA, the active metabolite of 2-ME). In JRST, spermatocyte degeneration was morphol. obvious 19 h after a 5-h exposure to 5 mM MAA. The lesion was unaffected by the presence or absence of extratubular Ca2+. However, MAA-induced **cell death** was significantly prevented by co-treatment with the dihydropyridines (DHP) nifedipine (50 μM) and nicardipine (20 μM), as well as verapamil (50 μM) and TMB-8 (50 μM), all of which are able to inhibit calcium movement through plasma membranes. However, neither ryanodine, dantrolene, nor cyclosporin A and ruthenium red, which inhibit Ca2+ mobilization from intracellular stores (endoplasmic reticulum and mitochondria), affected the MAA-induced **cell death**. Inhibition of calcium mobilization through IP3-sensitive pathways by blocking the product of IP3 with manoalide, neomycin, and U73122 did not block the MAA-induced lesion. The protective effects of 50 μM nifedipine and 50 μM TMB-8 were also observed in ARSTs treated with 10 mM MAA for 5 h. However, when rat testicular sections were immunohistochem. stained with monoclonal antibodies specific for the α1 (the DHP receptor) or the α2 subunits of DHP-sensitive calcium channels, no pos. staining was found. Finally, in an attempt to see whether the intracellular free calcium concns. ([Ca2+]i) in germ cells were increased after the MAA treatment, intact seminiferous tubules were loaded with indo-1 and were measured using laser-scanning confocal microscopy. No detectable increase in the signal in MAA-sensitive spermatocytes was observed, while a 34-54% increase in the signal could be detected in the same cell types when tubules were exposed to 10 μM of the calcium ionophore 4-bromo-A23187 for 5 min. Collectively, these data suggest that the protective effect of calcium channel blockers against the MAA-induced spermatocyte **apoptosis** is probably not through their blocking effect on DHP-sensitive calcium channels. We postulate alternate mechanisms based on stabilization of cell membranes or interactions with calmodulin or protein kinase C.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 35 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:592359 HCAPLUS
DOCUMENT NUMBER: 127:276129
TITLE: Role of env in HIV-mediated **apoptosis**
AUTHOR(S): Koga, Yasuhiro; Sasaki, Masafumi
CORPORATE SOURCE: Dept. of Infectious Diseases, Tokai Univ. School of Medicine, Kanagawa, 259-11, Japan
SOURCE: Uirusu (1997), 47(1), 99-107
CODEN: UIRUAF; ISSN: 0042-6857
PUBLISHER: Nippon Uirusu Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 48 refs., on establishment of HIV infection, disappearance of CD4+ T cells in HIV direct infection, role of gp160 and **calmodulin** and **calcium** in **apoptosis** and **cell death**, and **apoptosis** in noninfectious cells.

L9 ANSWER 36 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:581525 HCAPLUS
DOCUMENT NUMBER: 127:174510
TITLE: The effect of calmodulin antagonist (chlorpromazine hydrochloride) on the morphology and viability of human decidual cells in culture
AUTHOR(S): Leng, Ying; Yang, Renzhu
CORPORATE SOURCE: Dep. Biology, Nanjing Normal Univ., Nanjing, 210097, Peop. Rep. China
SOURCE: Shengzhi Yu Biyun (1997), 17(2), 76-81
CODEN: SCYYDZ; ISSN: 0253-357X
PUBLISHER: Shengzhi Yu Biyun Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB The effect of calmodulin antagonist-chlorpromazine hydrochloride (CPZ) and calcium chelate EGTA on the morphol. and viability of human decidual cells wee studied by cell culture technique. The morphol. of the cells was greatly changed and the viability was significantly inhibited when the decidual cells were preincubated with CPZ (>=20 mol·L-1) or/and EGTA (>=2 mmol·L-1) for a certain time. The higher the concentration and the longer the time was, the more significant inhibition was. The presence of EGTA significantly enhanced the inhibition of CPZ on the viability of decidual cells. The results suggest that Ca2+-CaM system may be directly involved in the decidual development and maintenance.

L9 ANSWER 37 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:576924 HCAPLUS
DOCUMENT NUMBER: 125:245444
TITLE: Role of calmodulin in HIV-potentiated Fas-mediated **apoptosis**
AUTHOR(S): Pan, Zhiqi; Radding, Wilson; Zhou, Tong; Hunter, Eric; Mountz, John; McDonald, Jay M.
CORPORATE SOURCE: Department of Pathology, University of Alabama, Birmingham, AL, 35294-0007, USA
SOURCE: American Journal of Pathology (1996), 149(3), 903-910
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The recently demonstrated extraordinary rate of turnover of T cells in human immunodeficiency virus (HIV)-1-infected patients and the apparently concomitant high rate of viral production and death are consistent with a large amount of **cell death** directly due to infection. **Apoptosis** may be one of the major forms of T **cell death** in HIV-1 infection. Many apoptotic pathways depend on calcium and therefore would be expected to involve calmodulin. As the HIV-1 envelope glycoprotein, gp160, contains two known calmodulin-binding domains, we investigated the possibility that the cytoplasmic domain of the HIV-1 envelope protein gp160 could enhance Fas-mediated **apoptosis**, the major form of **apoptosis** in lymphocytes.

Our studies have shown that (1) transfection of H9 and MOLT-4 cells with a non-infectious HIV proviral clone, pFN, which expresses wild-type gp160, leads to enhanced Fas-mediated **apoptosis**, (2) transfection of MOLT-4 cells with a pFN construct pFNΔ147, which expresses a carboxyl-terminally truncated gp160 lacking the calmodulin-binding domains, produces less Fas-mediated **apoptosis** than transfection with pFN, and (3) the calmodulin antagonists trifluoperazine and tamoxifen completely inhibit the pFN enhancement of Fas-mediated **apoptosis** in MOLT-4 cells. We have replicated all of these results using the vectors pSRHS and pSRHSΔ147, which express wild-type gp160 and truncated gp160, resp., in the absence of other viral proteins. These investigations provide a mechanism by which HIV-1 may induce **apoptosis** and a possible intracellular target for future therapeutics.

L9 ANSWER 38 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:656602 HCAPLUS
DOCUMENT NUMBER: 125:297187
TITLE: Transduction of an ethylene signal is required for **cell death** and lysis in the root cortex of maize during aerenchyma formation induced by hypoxia
AUTHOR(S): He, Chuan-Jiu; Morgan, Page W.; Drew, Malcolm C.
CORPORATE SOURCE: Department Horticultural Sciences, Texas A&M University, College Station, TX, 77843, USA
SOURCE: Plant Physiology (1996), 112(2), 463-472
CODEN: PLPHAY; ISSN: 0032-0889
PUBLISHER: American Society of Plant Physiologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ethylene has been implicated in signaling **cell death** in the lysigenous formation of gas spaces (aerenchyma) in the cortex of adventitious roots of maize (Zea mays) subjected to hypoxia. Various antagonists that are known to modify particular steps in signal transduction in other plant systems were applied at low concns. to normoxic and hypoxic roots of maize, and the effect on **cell death** (aerenchyma formation) and the increase in cellulase activity that precedes the appearance of cell degeneration were measured. Both cellulase activity and **cell death** were inhibited in hypoxic roots in the presence of antagonists of inositol phospholipids, Ca2+-calmodulin, and protein kinases. By contrast, there was a parallel promotion of cellulase activity and **cell death** in hypoxic and normoxic roots by contact with reagents that activate G-proteins, increase cytosolic Ca2+, or inhibit protein phosphatases. Most of these reagents had no effect on ethylene biosynthesis and did not arrest root extension. These results indicate that the transduction of an ethylene signal leading to an increase in intracellular Ca2+ is necessary for **cell death** and the resulting aerenchyma development in roots of maize subjected to hypoxia.

L9 ANSWER 39 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:692773 HCAPLUS
DOCUMENT NUMBER: 126:54517
TITLE: Calcium in suramin-induced rat sensory neuron toxicity in vitro
AUTHOR(S): Sun, Xiaofeng; Windebank, Anthony J.
CORPORATE SOURCE: Department of Neurology, Mayo Clinic and Mayo Foundation, 1501 Guggenheim Building, 200 First Street SW, Rochester, MN, 55905, USA
SOURCE: Brain Research (1996), 742(1,2), 149-156
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Suramin is an exptl. chemotherapeutic agent and a neurotoxin which causes a dose-dependent peripheral neuropathy in vivo and inhibits dorsal root ganglion (DRG) neurite outgrowth in vitro. The mechanism of suramin-induced cyto- and neurotoxicity remains unclear. Calcium is a key signal transducer in cellular responses to a variety of physiol. and

pathogenic stimuli. In the present study, we have determined the role of calcium in suramin-induced neurotoxicity in dorsal root ganglion neurons in vitro. Suramin-induced inhibition of neurite outgrowth and induction of neuronal **cell death** were dose-related phenomena. A low level of extracellular calcium significantly reduced suramin-induced inhibition of neurite outgrowth and delayed neuronal **cell death** in vitro. Nimodipine (100 μM), an L-type voltage-sensitive calcium channel (VSCC) inhibitor, mimicked low calcium medium and protected neurite outgrowth in regular calcium medium supplemented with 300 μM suramin. TMB-8 (100 μM), an inhibitor of intracellular calcium release, failed to protect neurite outgrowth against the toxin. Calmidazolium (10 μM), a potent calmodulin inhibitor, and calpain inhibitor peptide (CIP, 10 μM) protected neurite outgrowth against suramin. The results support the hypothesis that the calcium signaling system is important in suramin-induced neurotoxicity. Influx of extracellular calcium is more important than release of intracellular calcium in causing cell injury in vitro.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 40 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:406660 HCAPLUS
DOCUMENT NUMBER: 125:132121
TITLE: Calcium channel blockers induce thymic **apoptosis** in vivo in rats
AUTHOR(S): Balakumaran, Arun; Campbell, Gerald A.; Moslen, Mary Treinen
CORPORATE SOURCE: Dep. of Pathology, Univ. of Texas Medical Branch, Galveston, TX, 77555-0605, USA
SOURCE: Toxicology and Applied Pharmacology (1996), 139(1), 122-127
CODEN: TXAPA9; ISSN: 0041-008X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We investigated the in vivo effect of structurally different calcium channel blockers (CCB) on rat thymus. Administration of verapamil (40 mg/kg i.p.), diltiazem (90 mg/kg i.p.), nifedipine (15 mg/kg i.p.), or nicardipine (10 mg/kg i.p.) induced apoptotic indexes of 4.3, 4.0, 2.0, and 6.5, resp., compared to 0.5 in the saline-treated control rats. **Apoptosis** was assessed by morphol. and the apoptotic index was calculated using a computer-assisted image analyzer. Diltiazem had a rapid and substantial effects as evidenced by **apoptosis** at 1.5 h and a 36% decrease in thymus weight by 24 h. We were uncertain about the mechanisms by which CCB induced thymic **apoptosis** in vivo since in vitro studies have shown that increases in intracellular calcium cause **apoptosis** and that CCB prevent **apoptosis**. We sought insight into the mechanism by evaluating potential and known in vivo effects of these drugs. Neither verapamil nor diltiazem was found to elevate serum cortisol levels, a known trigger for **apoptosis**. Hypotension, a known response to CCB, does not appear to be causal factor since the potent hypotensive agent sodium nitroprusside (10 μg/kg, i.v.) did not cause a significant increase in thymic **apoptosis**. Calcium signaling may be important since the calmodulin antagonist chlorpromazine (60 mg/kg i.p.) was found to induce a 15-fold increase in **apoptosis**. Our observations suggest that calcium signaling is necessary for the survival of the T lymphocytes in the thymus.

L9 ANSWER 41 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:640769 HCAPLUS
DOCUMENT NUMBER: 125:273467
TITLE: Induction of **apoptosis** by calmodulin-dependent intracellular Ca2+ elevation in CD4+ cells expressing gp160 of HIV
AUTHOR(S): Sasaki, Masafumi; Uchiyama, Junzo; Ishikawa, Hiroki; Matsushita, Shuzo; Kimura, Genki; Nomoto, Kikuo; Koga, Yasuhiro
CORPORATE SOURCE: Dep. Virology, Dep. Immunology, Med. Inst. Bioregulation, Kyushu Univ., Fukuoka, 812, Japan

SOURCE: Virology (1996), 224(1), 18-24
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human CD4+ cell clones expressing either gp160 or gp120 of HIV-1 under the transcriptional control of an inducible promoter were used to examine the role of Ca2+ signaling in the induction of **apoptosis** by envelope glycoproteins. Single-cell killing with **apoptosis** was induced in the cells expressing gp160 while no such **apoptosis** was found in the cell expressing gp120. An increase of intracellular Ca2+ was found in the gp160-expressing cells but not in the gp120-expressing cells as determined by intracellular Ca2+ imaging anal. before the appearance of DNA fragmentation. W7, a calmodulin antagonist, blocked the elevation of Ca2+ as well as the resultant DNA fragmentation, which thus implies that the calmodulin-dependent intracellular Ca2+ release system is first activated by gp160 and thereafter **apoptosis** takes place. Thus, Ca2+ signaling plays a crucial role in the **apoptosis** accompanying the single-**cell death** induced by gp160 in CD4+ cells.

L9 ANSWER 42 OF 48 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 95232497 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7716515
TITLE: Calcium signaling in neurons: molecular mechanisms and cellular consequences.
AUTHOR: Ghosh A; Greenberg M E
CORPORATE SOURCE: Department of Neurology, Children's Hospital, Boston, MA 02115, USA.
CONTRACT NUMBER: NS28829 (NINDS)
SOURCE: Science, (1995 Apr 14) 268 (5208) 239-47. Ref: 66
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950524
Last Updated on STN: 19950524
Entered Medline: 19950512

AB Neuronal activity can lead to marked increases in the concentration of cytosolic calcium, which then functions as a second messenger that mediates a wide range of cellular responses. Calcium binds to calmodulin and stimulates the activity of a variety of enzymes, including calcium-**calmodulin** kinases and **calcium**-sensitive adenylate cyclases. These enzymes transduce the calcium signal and effect short-term biological responses, such as the modification of synaptic proteins and long-lasting neuronal responses that require changes in gene expression. Recent studies of calcium signal-transduction mechanisms have revealed that, depending on the route of entry into a neuron, calcium differentially affects processes that are central to the development and plasticity of the nervous system, including activity-dependent cell survival, modulation of synaptic strength, and calcium-mediated **cell death**.

L9 ANSWER 43 OF 48 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 1994:658462 SCISEARCH
THE GENUINE ARTICLE: PK334
TITLE: DOMOIC ACID INHIBITS ADENYLATE-CYCLASE ACTIVITY IN RAT-BRAIN MEMBRANES
AUTHOR: NIJJAR M S (Reprint); GRIMMELT B
CORPORATE SOURCE: UNIV PRINCE EDWARD ISL, ATLANTIC VET COLL, DEPT ANAT & PHYSIOL, TOXICOL LAB, 550 UNIV AVE, CHARLOTTETOWN C1A 4P3, PE, CANADA (Reprint)
COUNTRY OF AUTHOR: CANADA
SOURCE: MOLECULAR AND CELLULAR BIOCHEMISTRY, (27 JUL 1994) Vol. 136, No. 2, pp. 105-111.

ISSN: 0300-8177.
PUBLISHER: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA DORDRECHT, NETHERLANDS.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 30
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Adenylate cyclase activity measured by the formation of cyclic AMP in rat brain membranes was inhibited by a shellfish toxin, domoic acid (DOM). The inhibition of enzyme was dependent on DOM concentration, but about 50% of enzyme activity was resistant to DOM-induced inhibition. Rat brain supernatant resulting from 105,000 x g centrifugation for 60 min, stimulated adenylate cyclase activity in membranes. Domoic acid abolished the supernatant-stimulated adenylate cyclase activity. The brain supernatant contains factors which modulate adenylate cyclase activity in membranes. The stimulatory factors include calcium, calmodulin, and GTP, In view of these findings, we examined the role of calcium and calmodulin in DOM-induced inhibition of adenylate cyclase in brain membranes. Calcium stimulated adenylate cyclase activity in membranes, and further addition of **calmodulin** potentiated **calcium**-stimulated enzyme activity in a concentration dependent manner. Calmodulin also stimulated adenylate cyclase activity, but further addition of calcium did not potentiate calmodulin-stimulated enzyme activity. These results show that the rat brain membranes contain endogenous calcium and calmodulin which stimulate adenylate cyclase activity. However, calmodulin appears to be present in membranes in sub-optimal concentration for adenylate cyclase activation, whereas calcium is present at saturating concentration. Adenylate cyclase activity diminished as DOM concentration was increased, reaching a nadir at about 1 mM. Addition of calcium restored DOM-inhibited adenylate cyclase activity to the control level. Similarly, EGTA also inhibited adenylate cyclase activity in brain membranes in a concentration dependent manner, and addition of calcium restored EGTA-inhibited enzyme activity to above control level. The fact that EGTA is a specific chelator of calcium, and that DOM mimicked adenylate cyclase inhibition by EGTA, indicate that calcium mediates DOM-induced inhibition of adenylate cyclase activity in brain membranes. While DOM completely abolished the supernatant-, and Gpp(NH)p-stimulated adenylate cyclase activity, it partly blocked calmodulin-, and forskolin-stimulated adenylate cyclase activity in brain membranes. These results indicate that DOM may interact with guanine nucleotide-binding (G) protein and/or the catalytic subunit of adenylate cyclase to produce inhibition of enzyme in rat brain membranes.

L9 ANSWER 44 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:558197 HCAPLUS
DOCUMENT NUMBER: 119:158197
TITLE: Transient elevations of cytosolic free calcium retard subsequent **apoptosis** in neutrophils in vitro
AUTHOR(S): Whyte, Moira K. B.; Hardwick, Simon J.; Meagher, Laura C.; Savill, John S.; Haslett, Christopher
CORPORATE SOURCE: R. Postgrad. Med. Sch., Hammersmith Hosp., London, W12 ONN, UK
SOURCE: Journal of Clinical Investigation (1993), 92(1), 446-55
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Elevation of cytosolic calcium ([Ca2+]i) has been reported to induce **apoptosis** in a number of cell types. However, in the neutrophil, which undergoes **apoptosis** constitutively during aging in vitro, activation by inflammatory mediators elevates [Ca2+]i and prolongs lifespan via inhibition of **apoptosis**. To examine this paradox, the authors investigated the effects of modulation of [Ca2+]i upon **apoptosis** of neutrophils in vitro. Calcium ionophores (A23187, ionomycin) retarded **apoptosis** in neutrophil populations after 20 h. Conversely, intracellular Ca2+-chelation, using BAPTA acetoxymethyl

ester (AM) promoted **apoptosis**. W-7 (an inhibitor of calmodulin) also promoted **apoptosis**. Measurements of [Ca2+]i, using fura-2, showed: (a) increased **apoptosis** in neutrophil populations was not associated with elevated [Ca2+]i, (b) neutrophils cultured with ionophore at concns. inhibiting **apoptosis** exhibited transient (<1 h) elevations of [Ca2+]i, to levels previously reported with receptor-mediated stimuli, and (c) BAPTA was able to prevent the elevation of [Ca2+]i and the inhibition of **apoptosis** produced by ionophore. Modulation of **apoptosis** occurred without alterations in intracellular pH. Thus, in the neutrophil, unlike lymphoid cells, elevation of [Ca2+]i exerts an inhibitory effect upon **apoptosis**. These data suggest that transient elevation of [Ca2+]i elicits signaling events leading to prolonged inhibition of **apoptosis**.

L9 ANSWER 45 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:166565 HCAPLUS
DOCUMENT NUMBER: 118:166565
TITLE: Role of calcium in inactivation of calcium/calmodulin dependent protein kinase II after cerebral ischemia
AUTHOR(S): Hiestand, David M.; Haley, Boyd E.; Kindy, Mark S.
CORPORATE SOURCE: Dep. Biochem., Univ. Kentucky, Lexington, KY, 40536-0084, USA
SOURCE: Journal of the Neurological Sciences (1992), 113(1), 31-7
CODEN: JNSCAG; ISSN: 0022-510X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Transient cerebral ischemia demonstrates an increase in activated oxygen species in the brain that could lead to eventual neuronal **cell death**. Neuronal cells respond to oxygen free radicals through the restructuring of the cytoskeleton and membranes, mobilization of calcium and gene expression which play a role in cell injury. Ten min of bilateral carotid artery occlusion resulted in a decrease in calcium/calmodulin dependent protein kinase II (CaM kinase II) phosphorylation and activity detected in the brain immediately following ischemia and was partially restored within 24 h of reperfusion. Pretreatment of animals with an anesthetic dose of pentobarbital (40 mg/kg) resulted in partial protection of inactivation of CaM kinase II following ischemia. CaM kinase II activity was maintained following pretreatment of animals with α-Ph N-tert-Bu nitrone (PBN), which traps oxygen free radicals. Infusion of superoxide dismutase or catalase prior to ischemia, blocked CaM kinase II inactivation. Blockage of calcium uptake with bepridil resulted in a marked protection of CaM kinase II inactivation. In addition, trifluoperazine, a calmodulin antagonist also diminished the inhibition of CaM kinase II phosphorylation in our model. Apparently, ischemia and reperfusion injury results in the generation of activated oxygen and the mobilization of calcium which inactivate CaM kinase II. Changes associated with protein kinase activity in the brain following an ischemic insult may have profound effects upon neurodegeneration and neuronal survival.

L9 ANSWER 46 OF 48 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 91222238 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2025284
TITLE: A DNA crosslinking drug alters synthesis of several low molecular weight proteins in human lymphoma cells.
AUTHOR: Widstrom R L; Ducore J M
CORPORATE SOURCE: Department of Pediatrics, School of Medicine, University of California, Davis 95616.
CONTRACT NUMBER: CA-41265 (NCI)
SOURCE: Biochemical and biophysical research communications, (1991 Apr 30) 176 (2) 717-21.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199106
ENTRY DATE: Entered STN: 19910623

Last Updated on STN: 19980206
Entered Medline: 19910606

AB The cytotoxicity of bifunctional alkylating agents is generally attributed to DNA damage, especially DNA-DNA crosslinking activity. It is unclear how crosslinks or other cellular damage result in **cell death**. Studies of drug effects at the level of expression of specific gene products may help elucidate the mechanism of cell killing. We examined proteins synthesized in L-phenylalanine mustard treated human lymphoma cells by [35S]methionine labeling and SDS-PAGE. Drug-treated cells showed decreased labeling of proteins in two molecular weight bands of 17 kDa (a doublet) and 12 kDa at 6, 18 and 24 hours after drug removal. One of the components of the 17 kDa doublet has been identified as **calmodulin**, a **calcium** binding protein essential to cell cycle progression and survival.

L9 ANSWER 47 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:207961 HCAPLUS
DOCUMENT NUMBER: 110:207961
TITLE: Calcium-activated DNA fragmentation in rat liver nuclei
AUTHOR(S): Jones, Dean P.; McConkey, David J.; Nicotera, Pierluigi; Orrenius, Sten
CORPORATE SOURCE: Dep. Toxicol., Karolinska Inst., Stockholm, S-10401, Swed.
SOURCE: Journal of Biological Chemistry (1989), 264(11), 6398-403
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Incubation of isolated rat liver nuclei with ATP, NAD+, and submicromolar Ca2+ concns. resulted in extensive DNA hydrolysis. Half-maximal activity occurred with 200 nM Ca2+, and saturation of the process was observed with 1 μM Ca2+. ATP stimulated a calmodulin-dependent nuclear Ca2+ uptake system which apparently mediated endonuclease activation. Ca2+-activated DNA fragmentation was inhibited by the inhibitor of poly(ADP-ribose) synthetase, 3-aminobenzamide, and was associated with poly(ADP-ribosyl)ation of nuclear protein. The characteristics of this endonuclease activity indicate that it may be responsible for the Ca2+-dependent fragmentation of DNA involved in programmed **cell death** (**apoptosis**) and in certain forms of chemical induced cell killing.

L9 ANSWER 48 OF 48 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1985:125348 HCAPLUS
DOCUMENT NUMBER: 102:125348
TITLE: Phenothiazine suppression of transient depolarizations in rabbit ventricular cells
AUTHOR(S): Kremers, M. S.; Kenyon, J. L.; Ito, K.; Sutko, J. L.
CORPORATE SOURCE: Health Sci. Cent. Dallas, Univ. Texas, Dallas, TX, 75235, USA
SOURCE: American Journal of Physiology (1985), 248(2, Pt. 2), H291-H296
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Trifluperazine [117-89-5] and fluphenazine [69-23-8] effectively abolished arrhythmogenic transient depolarizations and prevented or delayed **cell death** caused by Ca overload in rabbit ventricular cells. While the mechanism for this action is not established, the effect is strong and is expected to be the basis of a marked antiarrhythmic action of these compds. The data suggest that Ca-calmodulin-dependent processes may play a role in the generation of Ca-overload-induced arrhythmias.

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(FILE 'HOME' ENTERED AT 16:20:43 ON 18 AUG 2005)

FILE 'STNGUIDE' ENTERED AT 16:20:51 ON 18 AUG 2005

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     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 16:21:28 ON 18 AUG 2005
L1        128381 S CALMODULIN
L2       2167794 S CALCIUM
L3          5710 S L1 (2W) L2
L4          1485 S L3 AND KINASE?
L5           149 S "DRP-1"
L6             1 S L3 AND L5
L7        712168 S APOPTOSIS OR (CELL(A)DEATH)
L8            66 S L3 AND L7
L9            48 DUP REM L8 (18 DUPLICATES REMOVED)

=> s l9 and "dap(w)kinase?"
L10            0 L9 AND "DAP(W)KINASE?"

=> s dap(2w)kinase?
L11          922 DAP(2W) KINASE?

=> s l5 and l11
L12           30 L5 AND L11

=> dup rem l12
PROCESSING COMPLETED FOR L12
L13            9 DUP REM L12 (21 DUPLICATES REMOVED)

=> d 1-9 ibib ab

L13  ANSWER 1 OF 9  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:673387  HCAPLUS
TITLE:                    Soluble immunotoxin complex comprising catalytically
                          active kinase (immunokinase), nucleic acids encoding
                          the same, and therapeutic, diagnostic and analytical
                          uses thereof
INVENTOR(S):              Barth, Stefan; Tur, Mehmet Kemal; Stoecker, Michael;
                          Fischer, Rainer
PATENT ASSIGNEE(S):       Fraunhofer Gesellschaft zur Foerderung der Angewandten
                          Forschung e.V., Germany
SOURCE:                   PCT Int. Appl., 64 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2005068616         A2    20050728    WO 2005-EP50131         20050113
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                       EP 2004-847          A  20040116
                                             EP 2004-17928        A  20040729
AB   The inventors found that soluble, endogenous complexes - immunokinases -
     comprising cell-specific antibody fragment(s) which is/are linked to
     constantly and catalytically active kinase(s) that develop
     cytotoxic/regulative activity upon internalization of the complex are
     superior over state of the art immunotoxins.  Immunokinases are superior
     as immunotoxins in that they have a higher specificity combining specific
     binding to a target cell with specific constitutive catalytic activity
     inside the target cell, a reduced immunogenicity, an improved activity and
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are resistant to non-specific inactivation, and are thus are less prone to activity reduction The invention provides a synthetic, soluble, endogenous complex formed from at least one component A and at least one component B, whereby component A comprises a binding domain for extra-cellular surface structures that internalize upon binding of component A of said complex, and component B has a constitutive catalytic kinase activity and effects cell biosynthesis/signalling including cell death after internalization. The complex allows to influence the growth and the physiol. of cells. In particular said complex, nucleic acid mols. encoding it, cells transfected or transformed with these nucleic acid mols. are usable for the preparation of medicaments for the treatment of proliferative diseases, inflammatory diseases, allergies and autoimmune diseases. The invention further relates to a medicament comprising said complex, nucleic acids, vectors, cells or organisms. Furthermore the complexes, nucleic acids, vectors, cells and kits of the present invention are usable in prognostic, diagnostic and analytic kinase assays.

L13 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:555758 HCAPLUS
DOCUMENT NUMBER: 139:286763
TITLE: Gene array analysis of bone morphogenetic protein type I receptor-induced osteoblast differentiation
AUTHOR(S): Korchynskyi, Olexander; Dechering, Koen J.; Sijbers, Anneke M.; Olijve, Wiebe; Ten Dijke, Peter
CORPORATE SOURCE: Division of Cellular Biochemistry, The Netherlands Cancer Institute, Amsterdam, Neth.
SOURCE: Journal of Bone and Mineral Research (2003), 18(7), 1177-1185
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: American Society for Bone and Mineral Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The genomic response to BMP was investigated by ectopic expression of activated BMP type I receptors in C2C12 myoblast using cDNA microarrays. Novel BMP receptor target genes with possible roles in inhibition of myoblast differentiation and stimulation of osteoblast differentiation were identified. Bone morphogenetic proteins (BMPs) have an important role in controlling mesenchymal cell fate and mediate these effects by regulating gene expression. BMPs signal through three distinct specific BMP type I receptors (also termed activin receptor-like kinases) and their downstream nuclear effectors, termed Smads. The critical target genes by which activated BMP receptors mediate change cell fate are poorly characterized. We performed transcriptional profiling of C2C12 myoblasts differentiation into osteoblast-like cells by ectopic expression of three distinct constitutively active (ca)BMP type I receptors using adenoviral gene transfer. Cells were harvested 48 h after infection, which allowed detection of both early and late response genes. Expression anal. was performed using the mouse GEM1 microarray, which is comprised of approx. 8700 unique sequences. Hybridizations were performed in duplicate with a reverse fluor labeling. Genes were considered to be significantly regulated if the p value for differential expression was less than 0.01 and inverted expression ratios per duplicate successful reciprocal hybridizations differed by less than 25%. Each of the three caBMP type I receptors stimulated equal levels of R-Smad phosphorylation and alkaline phosphatase activity, an early marker for osteoblast differentiation. Interestingly, all three type I receptors induced identical transcriptional profiles; 97 genes were significantly upregulated and 103 genes were downregulated. Many extracellular matrix genes were upregulated, muscle-related genes downregulated, and transcription factors/signaling components modulated. In addition to 41 expressed sequence tags without known function and a number of known BMP target genes, including PPAR-γ and fibromodulin, a large number of novel BMP target genes with an annotated function were identified, including transcription factors HesR1, ITF-2, and ICSBP, apoptosis mediators DRP-1 death kinase and ZIP kinase, IκBα, Edg-2, ZO-1, and E3 ligase Dactylin. These target genes, some of them unexpected, offer new insights into how BMPs elicit biol. effects, in particular into the mechanism of inhibition of myoblast differentiation and stimulation of osteoblast differentiation.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:559464 HCAPLUS
DOCUMENT NUMBER: 140:89347
TITLE: Type II autophagic cell death and death-associated protein kinases
AUTHOR(S): Saelens, Xavier; Vondenabeele, Peter
CORPORATE SOURCE: Ghent University, Belg.
SOURCE: Chemtracts (2003), 16(6), 387-392
CODEN: CHEMFW; ISSN: 1431-9268
PUBLISHER: Data Trace Publishing Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review on death-associated protein kinase (DAPk or **DAP-kinase**) and DAPk-related protein kinase (**DRP-1**) as possible signaling mols. in type II autophagic cell death. **DAP-kinase** and **DRP-1** are calmodulin-regulated Ser/Thr protein kinases belonging to the family of nonmuscle myosin light chain kinases. The caspase-independent and caspase-dependent effects of these protein kinases are discussed.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 9 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2002243327 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11980920
TITLE: **DAP kinase** and **DRP-1** mediate membrane blebbing and the formation of autophagic vesicles during programmed cell death.
AUTHOR: Inbal Boaz; Bialik Shani; Sabanay Ilana; Shani Gidi; Kimchi Adi
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: Journal of cell biology, (2002 Apr 29) 157 (3) 455-68. Electronic Publication: 2002-04-29. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020501
Last Updated on STN: 20030105
Entered Medline: 20020522
AB Death-associated protein kinase (DAPk) and DAPk-related protein kinase (**DRP**)-**1** proteins are Ca+2/calmodulin-regulated Ser/Thr death kinases whose precise roles in programmed cell death are still mostly unknown. In this study, we dissected the subcellular events in which these kinases are involved during cell death. Expression of each of these DAPk subfamily members in their activated forms triggered two major cytoplasmic events: membrane blebbing, characteristic of several types of cell death, and extensive autophagy, which is typical of autophagic (type II) programmed cell death. These two different cellular outcomes were totally independent of caspase activity. It was also found that dominant negative mutants of DAPk or **DRP-1** reduced membrane blebbing during the p55/tumor necrosis factor receptor 1-induced type I apoptosis but did not prevent nuclear fragmentation. In addition, expression of the dominant negative mutant of **DRP-1** or of DAPk antisense mRNA reduced autophagy induced by antiestrogens, amino acid starvation, or administration of interferon-gamma. Thus, both endogenous DAPk and **DRP-1** possess rate-limiting functions in these two distinct cytoplasmic events. Finally, immunogold staining showed that **DRP-1** is localized inside the autophagic vesicles, suggesting a direct involvement of this kinase in the process of autophagy.

L13 ANSWER 5 OF 9 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2002687075 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12445458
TITLE: The **DAP-kinase** family of proteins: study of a novel group of calcium-regulated death-promoting kinases.
AUTHOR: Shohat Galit; Shani Gidi; Eisenstein Miriam; Kimchi Adi
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, 76100, Rehovot, Israel.
SOURCE: Biochimica et biophysica acta, (2002 Nov 4) 1600 (1-2) 45-50. Ref: 15
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021214
Last Updated on STN: 20030102
Entered Medline: 20021231

AB **DAP-kinase** (DAPk) is a Ca(2+)/calmodulin (CaM)-regulated Ser/Thr kinase that functions as a positive mediator of programmed cell death. It associates with actin microfilament and has a unique multidomain structure. One of the substrates of DAPk was identified as myosin light chain (MLC), the phosphorylation of which mediates membrane blebbing. Four additional kinases have been identified based on the high homology of their catalytic domain to that of DAPk. Yet, they differ in the structure of their extracatalytic domains and in their intracellular localization. One member of this family, **DRP-1**, also shares with DAPk both the property of activation by Ca(2+)/CaM and a specific phosphorylation-based regulatory mechanism. The latter involves an inhibitory type of autophosphorylation on a conserved serine at position 308, in the CaM regulatory domains of these two kinases. This phosphorylation, which occurs in growing cells, restrains the death-promoting effects of these kinases, and is specifically removed upon exposure of cells to various apoptotic stimuli. The dephosphorylation at this site increases the binding and sensitivity of each of these two kinases to their common activator-CaM. In DAPk, the dephosphorylation of serine 308 also increases the Ca(2+)/CaM-independent substrate phosphorylation. In DPR-1, it also promotes the formation of homodimers necessary for its full activity. These results are consistent with a molecular model in which phosphorylation on serine 308 stabilizes a locked conformation of the CaM regulatory domain within the catalytic cleft and simultaneously also interferes with CaM binding. In **DRP-1**, it introduces an additional locking device by preventing homodimerization. We propose that this unique mechanism of autoinhibition, evolved to keep these death-promoting kinases silent in healthy cells and ensures their activation only in response to apoptotic signals.

L13 ANSWER 6 OF 9 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001328399 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11279167
TITLE: rDrak1, a novel kinase related to apoptosis, is strongly expressed in active osteoclasts and induces apoptosis.
AUTHOR: Kojima H; Nemoto A; Uemura T; Honma R; Ogura M; Liu Y
CORPORATE SOURCE: Tissue Engineering Research Center (TERC), National Institute of Advanced Industrial Science and Technology (AIST), 1-1-1 Higashi, Tsukuba Ibaraki 305-8562, Japan.
SOURCE: Journal of biological chemistry, (2001 Jun 1) 276 (22) 19238-43. Electronic Publication: 2001-03-14.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB042195
ENTRY MONTH: 200107

ENTRY DATE: Entered STN: 20010730
Last Updated on STN: 20030105
Entered Medline: 20010726

AB This is the first report of a novel serine/threonine kinase, rabbit death-associated protein (**DAP**) **kinase**-related apoptosis-inducing protein kinase 1 (rDRAK1), involved in osteoclast apoptosis. We searched for osteoclast-specific genes from a cDNA library of highly enriched rabbit osteoclasts cultured on ivory. One of the cloned genes has a high homology with human DRAK1 (hDRAK1), which belongs to the **DAP kinase** subfamily of serine/threonine kinases. By screening a rabbit osteoclast cDNA library and 5'-RACE (rapid amplification of cDNA ends), we obtained a full length of this cDNA, termed rDRAK1. The sequencing data indicated that rDRAK1 has 88.0, 44.6, 38.7, and 42.3% identity with hDRAK1, **DAP kinase**, **DRP-1**, and ZIP (zipper-interacting protein) kinase, respectively. To clarify the role of DRAK1 in osteoclasts, we examined the effect of three osteoclast survival factors (interleukin-1, macrophage colony-stimulating factor, and osteoclast differentiation-inducing factor) on rDRAK1 mRNA expression and the effect of rDRAK1 overexpression on osteoclast apoptosis. The results suggested that these three survival factors were proved to inhibit rDRAK1 expression in rabbit osteoclasts. After transfection of a rDRAK1 expression vector into cultured osteoclasts, overexpressed rDRAK1 was localized exclusively to the nuclei and induced apoptosis. Hence, rDRAK1 may play an important role in the core apoptosis program in osteoclast.

L13 ANSWER 7 OF 9 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001216755 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11230133
TITLE: Autophosphorylation restrains the apoptotic activity of **DRP-1** kinase by controlling dimerization and calmodulin binding.
AUTHOR: Shani G; Henis-Korenblit S; Jona G; Gileadi O; Eisenstein M; Ziv T; Admon A; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: EMBO journal, (2001 Mar 1) 20 (5) 1099-113.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20020420
Entered Medline: 20010419

AB **DRP-1** is a pro-apoptotic Ca2+/calmodulin (CaM)-regulated serine/threonine kinase, recently isolated as a novel member of the **DAP-kinase** family of proteins. It contains a short extra-catalytic tail required for homodimerization. Here we identify a novel regulatory mechanism that controls its pro-apoptotic functions. It comprises a single autophosphorylation event mapped to Ser308 within the CaM regulatory domain. A negative charge at this site reduces both the binding to CaM and the formation of **DRP-1** homodimers. Conversely, the dephosphorylation of Ser308, which takes place in response to activated Fas or tumour necrosis factor-alpha death receptors, increases the formation of **DRP-1** dimers, facilitates the binding to CaM and activates the pro-apoptotic effects of the protein. Thus, the process of enzyme activation is controlled by two unlocking steps that must work in concert, i.e. dephosphorylation, which probably weakens the electrostatic interactions between the CaM regulatory domain and the catalytic cleft, and homodimerization. This mechanism of negative autophosphorylation provides a safety barrier that restrains the killing effects of **DRP-1**, and a target for efficient activation of the kinase by various apoptotic stimuli.

L13 ANSWER 8 OF 9 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2000094983 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10629061
TITLE: Death-associated protein kinase-related protein 1, a novel serine/threonine kinase involved in apoptosis.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: Molecular and cellular biology, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (**DAP**) **kinase**-related protein, **DRP-1**. **DRP-1** is a 42-kDa Ca(2+)/calmodulin (CaM)-regulated serine threonine kinase which shows high degree of homology to **DAP kinase**. The region of homology spans the catalytic domain and the CaM-regulatory region, whereas the remaining C-terminal part of the protein differs completely from **DAP kinase** and displays no homology to any known protein. The catalytic domain is also homologous to the recently identified ZIP kinase and to a lesser extent to the catalytic domains of DRAK1 and -2. Thus, **DAP kinase** **DRP-1**, ZIP kinase, and DRAK1/2 together form a novel subfamily of serine/threonine kinases. **DRP-1** is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory domain, was converted into a constitutively active kinase. Ectopically expressed **DRP-1** induced apoptosis in various types of cells. Cell killing by **DRP-1** was dependent on two features: the status of the catalytic activity, and the presence of the C-terminal 40 amino acids shown to be required for self-dimerization of the kinase. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the C-terminal tail in apoptosis and generated a "superkiller" mutant. A dominant negative fragment of **DAP kinase** encompassing the death domain was found to block apoptosis induced by **DRP-1**. Conversely, a catalytically inactive mutant of **DRP-1**, which functioned in a dominant negative manner, was significantly less effective in blocking cell death induced by **DAP kinase**. Possible functional connections between **DAP kinase** and **DRP-1** are discussed.

L13 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:811348 HCAPLUS
DOCUMENT NUMBER: 132:46958
TITLE: Cloning, sequence and therapeutic applications of cell death-promoting **DAP-kinase** related protein kinase **DRP-1** and
INVENTOR(S): Kimchi, Adi
PATENT ASSIGNEE(S): Yeda Research and Development Company Ltd., Israel; McInnis, Patricia A.
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966030	A1	19991223	WO 1999-US13411	19990615

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,

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            DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
            JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
            MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
            TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,
            MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
            ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
            CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
    AU 9944408           A1    20000105    AU 1999-44408          19990615
    GB 2354522           A1    20010328    GB 2001-660            19990615
    GB 2354522           B2    20040121
PRIORITY APPLN. INFO.:                     US 1998-89294P      P  19980615
                                           WO 1999-US13411     W  19990615
AB   A new protein kinase, DAP-Kinase related 1 protein (
     DRP-1), which is a novel homolog of DAP-
     kinase, has been isolated. and cDNA sequence and amino acid
     sequences of human DRP-1 are reported.  This novel
     calmodulin-dependent kinase is a cell death-promoting protein functioning
     in the biochem. pathway which involves DAP (death-associated protein)-kinase
     (e.g., forming a cascade of sequential kinases, one directly activating
     the other).  Alternatively, the two kinases may operate to promote cell
     death in parallel pathways.
REFERENCE COUNT:         3     THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> d his

     (FILE 'HOME' ENTERED AT 16:20:43 ON 18 AUG 2005)

     FILE 'STNGUIDE' ENTERED AT 16:20:51 ON 18 AUG 2005

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 16:21:28 ON 18 AUG 2005
L1        128381 S CALMODULIN
L2       2167794 S CALCIUM
L3          5710 S L1 (2W) L2
L4          1485 S L3 AND KINASE?
L5           149 S "DRP-1"
L6             1 S L3 AND L5
L7        712168 S APOPTOSIS OR (CELL(A)DEATH)
L8            66 S L3 AND L7
L9            48 DUP REM L8 (18 DUPLICATES REMOVED)
L10            0 S L9 AND "DAP(W)KINASE?"
L11          922 S DAP(2W)KINASE?
L12           30 S L5 AND L11
L13            9 DUP REM L12 (21 DUPLICATES REMOVED)

=> s l4 and "DAP
MISMATCHED QUOTE 'AND "DAP'
Quotation marks (or apostrophes) must be used in pairs,
one before and one after the expression you are setting
off or masking.

=> s l4 and "DAP"
L14            2 L4 AND "DAP"

=> d 1-2 ibib ab

L14  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2001:500771  HCAPLUS
DOCUMENT NUMBER:          135:175919
TITLE:                    Calcium-calmodulin signalling pathway up-regulates
                          glutamatergic synaptic function in non-pyramidal, fast
                          spiking rat hippocampal CA1 neurons
AUTHOR(S):                Wang, Jin-Hui; Kelly, Paul
CORPORATE SOURCE:         Department of Molecular Biosciences, University of
                          Kansas, Lawrence, KS, 66045, USA
SOURCE:                   Journal of Physiology (Cambridge, United Kingdom)
```

(2001), 533(2), 407-422
CODEN: JPHYA7; ISSN: 0022-3751
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The role of Ca2+-calmodulin (CaM) signaling cascades in modulating glutamatergic synaptic transmission on CA1 non-pyramidal fast-spiking neurons was investigated using whole-cell recording and perfusion in rat hippocampal slices. Paired stimuli (PS), consisting of postsynaptic depolarization to 0 mV and presynaptic stimulation at 1 Hz for 30 s, enhanced excitatory postsynaptic currents (EPSCs) on non-pyramidal neurons in the stratum pyramidale (SP). The potentiation was reduced by the extracellular application of D-amino-5-phosphonovaleric acid (**DAP** -5, 40 μM), and blocked by the postsynaptic perfusion of 1,2-bis(2-aminophenoxy)-ethane-N,N,N',N'-tetraacetic acid (BAPTA, 10 mM), a CaM-binding peptide (100 μM) or CaMKII(281-301) (an autoinhibitory peptide of CaM-dependent protein **kinases**, 100 μM). The application of adenophostin, an agonist of inositol trisphosphate receptors (IP3Rs) that evokes Ca2+ release, into SP non-pyramidal neurons via the patch pipet (1 μM) enhanced EPSCs and occluded PS-induced synaptic potentiation. The co-application of BAPTA (10 mM) with adenophostin blocked synaptic potentiation. In addition, Ca2+-CaM (40:10 μM) induced synaptic potentiation, which occluded PS-induced potentiation and was attenuated by introducing CaMKII(281-301)(100 μM). EPSCs were sensitive to an antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR). Application of Ca2+-CaM into SP non-pyramidal neurons induced the emergence of AMPAR-mediated EPSCs that were not evoked by low stimulus intensity before perfusion. Ca2+-CaM also increased the amplitude and frequency of spontaneous EPSCs. A scavenger of nitric oxide, carboxy-PTIO (30 μM in slice-perfusion solution), did not affect these increases in sEPSCs. The magnitude of PS-, adenophostin- or Ca2+-CaM-induced synaptic potentiation in SP non-pyramidal neurons increased during postnatal development. These results indicate that Ca2+-CaM signaling pathways in CA1 SP non-pyramidal neurons up-regulate glutamatergic synaptic transmission probably through the conversion of inactive-to-active synapses.
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:811348 HCAPLUS
DOCUMENT NUMBER: 132:46958
TITLE: Cloning, sequence and therapeutic applications of cell death-promoting **DAP-kinase** related protein **kinase** DRP-1 and
INVENTOR(S): Kimchi, Adi
PATENT ASSIGNEE(S): Yeda Research and Development Company Ltd., Israel; McInnis, Patricia A.
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966030	A1	19991223	WO 1999-US13411	19990615
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9944408	A1	20000105	AU 1999-44408	19990615
GB 2354522	A1	20010328	GB 2001-660	19990615

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     GB 2354522           B2    20040121
PRIORITY APPLN. INFO.:                      US 1998-89294P      P  19980615
                                            WO 1999-US13411     W  19990615
AB   A new protein kinase, DAP-Kinase related 1
     protein (DRP-1), which is a novel homolog of DAP-kinase
     , has been isolated. and cDNA sequence and amino acid sequences of human
     DRP-1 are reported.  This novel calmodulin-dependent kinase is a
     cell death-promoting protein functioning in the biochem. pathway which
     involves DAP (death-associated protein)-kinase (e.g.,
     forming a cascade of sequential kinases, one directly activating
     the other).  Alternatively, the two kinases may operate to
     promote cell death in parallel pathways.
REFERENCE COUNT:         3     THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> e kimchi a/au
E1            2     KIMCHHAYARASY P/AU
E2            2     KIMCHHAYARASY PHUONG/AU
E3          527 --> KIMCHI A/AU
E4            8     KIMCHI A */AU
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E6          163     KIMCHI ADI/AU
E7            1     KIMCHI ADY/AU
E8            1     KIMCHI ALAIN N/AU
E9          109     KIMCHI ASHER/AU
E10           5     KIMCHI B/AU
E11           2     KIMCHI BRACHA/AU
E12          24     KIMCHI D/AU

=> a e3
A IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> end
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:n

=> d his

     (FILE 'HOME' ENTERED AT 16:20:43 ON 18 AUG 2005)

     FILE 'STNGUIDE' ENTERED AT 16:20:51 ON 18 AUG 2005

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 16:21:28 ON 18 AUG 2005
L1        128381 S CALMODULIN
L2       2167794 S CALCIUM
L3          5710 S L1 (2W) L2
L4          1485 S L3 AND KINASE?
L5           149 S "DRP-1"
L6             1 S L3 AND L5
L7        712168 S APOPTOSIS OR (CELL(A)DEATH)
L8            66 S L3 AND L7
L9            48 DUP REM L8 (18 DUPLICATES REMOVED)
L10            0 S L9 AND "DAP(W)KINASE?"
L11          922 S DAP(2W)KINASE?
L12           30 S L5 AND L11
L13            9 DUP REM L12 (21 DUPLICATES REMOVED)
L14            2 S L4 AND "DAP"
                 E KIMCHI A/AU

=> s e3
L15         527 "KIMCHI A"/AU

=> s l4 or l5
L16        1633 L4 OR L5
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=> s l15 and l16
L17         11 L15 AND L16

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PROCESSING COMPLETED FOR L17
L18          4 DUP REM L17 (7 DUPLICATES REMOVED)

=> d 1-4 ibib ab
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L18 ANSWER 1 OF 4 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 1

ACCESSION NUMBER: 2002278596 EMBASE
TITLE: DAP kinase and **DRP-1** mediate membrane blebbing and the formation of autophagic vesicles during programmed cell death.
AUTHOR: Inbal B.; Bialik S.; Sabanay I.; Shani G.; **Kimchi A.**
CORPORATE SOURCE: A. Kimchi, Dept. of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel. Adi.kimchi@weizmann.ac.il
SOURCE: Journal of Cell Biology, (29 Apr 2002) Vol. 157, No. 3, pp. 455-468.
Refs: 48
ISSN: 0021-9525 CODEN: JCLBA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20020822
Last Updated on STN: 20020822

AB Death-associated protein kinase (DAPk) and DAPk-related protein kinase (**DRP**)-**1** proteins are Ca(+2)/ calmodulin-regulated Ser/Thr death kinases whose precise roles in programmed cell death are still mostly unknown. In this study, we dissected the subcellular events in which these kinases are involved during cell death. Expression of each of these DAPk subfamily members in their activated forms triggered two major cytoplasmic events: membrane blebbing, characteristic of several types of cell death, and extensive autophagy, which is typical of autophagic (type II) programmed cell death. These two different cellular outcomes were totally independent of caspase activity. It was also found that dominant negative mutants of DAPk or **DRP-1** reduced membrane blebbing during the p55/tumor necrosis factor receptor 1-induced type I apoptosis but did not prevent nuclear fragmentation. In addition, expression of the dominant negative mutant of **DRP-1** or of DAPk antisense mRNA reduced autophagy induced by antiestrogens, amino acid starvation, or administration of interferon-γ. Thus, both endogenous DAPk and **DRP-1** possess rate-limiting functions in these two distinct cytoplasmic events. Finally, immunogold staining showed that **DRP-1** is localized inside the autophagic vesicles, suggesting a direct involvement of this kinase in the process of autophagy.

L18 ANSWER 2 OF 4 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 2

ACCESSION NUMBER: 2004083114 EMBASE
TITLE: The DAP-kinase family of proteins: Study of a novel group of calcium-regulated death-promoting kinases.
AUTHOR: Shohat G.; Shani G.; Eisenstein M.; **Kimchi A.**
CORPORATE SOURCE: A. Kimchi, Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel. Adi.kimchi@weizmann.ac.il
SOURCE: Biochimica et Biophysica Acta - Proteins and Proteomics, (4 Nov 2002) Vol. 1600, No. 1-2, pp. 45-50.
Refs: 15
ISSN: 1570-9639 CODEN: BBAPBW
PUBLISHER IDENT.: S 1570-9639(02)00443-0
COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040318
Last Updated on STN: 20040318

AB DAP-kinase (DAPk) is a Ca(2+)/calmodulin (CaM)-regulated Ser/Thr kinase that functions as a positive mediator of programmed cell death. It associates with actin microfilament and has a unique multidomain structure. One of the substrates of DAPk was identified as myosin light chain (MLC), the phosphorylation of which mediates membrane blebbing. Four additional kinases have been identified based on the high homology of their catalytic domain to that of DAPk. Yet, they differ in the structure of their extracatalytic domains and in their intracellular localization. One member of this family, **DRP-1**, also shares with DAPk both the property of activation by Ca(2+)/CaM and a specific phosphorylation-based regulatory mechanism. The latter involves an inhibitory type of autophosphorylation on a conserved serine at position 308, in the CaM regulatory domains of these two kinases. This phosphorylation, which occurs in growing cells, restrains the death-promoting effects of these kinases, and is specifically removed upon exposure of cells to various apoptotic stimuli. The dephosphorylation at this site increases the binding and sensitivity of each of these two kinases to their common activator - CaM. In DAPk, the dephosphorylation of serine 308 also increases the Ca (2+)/CaM-independent substrate phosphorylation. In DPR-1, it also promotes the formation of homodimers necessary for its full activity. These results are consistent with a molecular model in which phosphorylation on serine 308 stabilizes a locked conformation of the CaM regulatory domain within the catalytic cleft and simultaneously also interferes with CaM binding. In **DRP-1**, it introduces an additional locking device by preventing homodimerization. We propose that this unique mechanism of autoinhibition, evolved to keep these death-promoting kinases silent in healthy cells and ensures their activation only in response to apoptotic signals.

L18 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001216755 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11230133
TITLE: Autophosphorylation restrains the apoptotic activity of **DRP-1** kinase by controlling dimerization and calmodulin binding.
AUTHOR: Shani G; Henis-Korenblit S; Jona G; Gileadi O; Eisenstein M; Ziv T; Admon A; **Kimchi A**
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: EMBO journal, (2001 Mar 1) 20 (5) 1099-113.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20020420
Entered Medline: 20010419

AB **DRP-1** is a pro-apoptotic Ca2+/calmodulin (CaM)-regulated serine/threonine kinase, recently isolated as a novel member of the DAP-kinase family of proteins. It contains a short extra-catalytic tail required for homodimerization. Here we identify a novel regulatory mechanism that controls its pro-apoptotic functions. It comprises a single autophosphorylation event mapped to Ser308 within the CaM regulatory domain. A negative charge at this site reduces both the binding to CaM and the formation of **DRP-1** homodimers. Conversely, the dephosphorylation of Ser308, which takes place in response to activated Fas or tumour necrosis factor-alpha death receptors, increases the formation of **DRP-1** dimers, facilitates the binding to CaM and activates the pro-apoptotic effects of the protein. Thus, the process of enzyme activation is controlled by two unlocking

steps that must work in concert, i.e. dephosphorylation, which probably weakens the electrostatic interactions between the CaM regulatory domain and the catalytic cleft, and homodimerization. This mechanism of negative autophosphorylation provides a safety barrier that restrains the killing effects of **DRP-1**, and a target for efficient activation of the kinase by various apoptotic stimuli.

L18 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10629061
TITLE: Death-associated protein kinase-related protein 1, a novel serine/threonine kinase involved in apoptosis.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; **Kimchi A**
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: Molecular and cellular biology, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) kinase-related protein, **DRP-1**. **DRP-1** is a 42-kDa Ca(2+)/calmodulin (CaM)-regulated serine threonine kinase which shows high degree of homology to DAP kinase. The region of homology spans the catalytic domain and the CaM-regulatory region, whereas the remaining C-terminal part of the protein differs completely from DAP kinase and displays no homology to any known protein. The catalytic domain is also homologous to the recently identified ZIP kinase and to a lesser extent to the catalytic domains of DRAK1 and -2. Thus, DAP kinase **DRP-1**, ZIP kinase, and DRAK1/2 together form a novel subfamily of serine/threonine kinases. **DRP-1** is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory domain, was converted into a constitutively active kinase. Ectopically expressed **DRP-1** induced apoptosis in various types of cells. Cell killing by **DRP-1** was dependent on two features: the status of the catalytic activity, and the presence of the C-terminal 40 amino acids shown to be required for self-dimerization of the kinase. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the C-terminal tail in apoptosis and generated a "superkiller" mutant. A dominant negative fragment of DAP kinase encompassing the death domain was found to block apoptosis induced by **DRP-1**. Conversely, a catalytically inactive mutant of **DRP-1**, which functioned in a dominant negative manner, was significantly less effective in blocking cell death induced by DAP kinase. Possible functional connections between DAP kinase and **DRP-1** are discussed.

=> d his

(FILE 'HOME' ENTERED AT 16:20:43 ON 18 AUG 2005)

FILE 'STNGUIDE' ENTERED AT 16:20:51 ON 18 AUG 2005

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 16:21:28 ON 18 AUG 2005
L1 128381 S CALMODULIN
L2 2167794 S CALCIUM
L3 5710 S L1 (2W) L2
L4 1485 S L3 AND KINASE?

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L5          149 S "DRP-1"
L6            1 S L3 AND L5
L7       712168 S APOPTOSIS OR (CELL(A)DEATH)
L8           66 S L3 AND L7
L9           48 DUP REM L8 (18 DUPLICATES REMOVED)
L10           0 S L9 AND "DAP(W)KINASE?"
L11         922 S DAP(2W)KINASE?
L12          30 S L5 AND L11
L13           9 DUP REM L12 (21 DUPLICATES REMOVED)
L14           2 S L4 AND "DAP"
                E KIMCHI A/AU
L15         527 S E3
L16        1633 S L4 OR L5
L17          11 S L15 AND L16
L18           4 DUP REM L17 (7 DUPLICATES REMOVED)
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	Issue Date	Pages	Document ID	Title
1	20050818	23	US 20050182016 A1	Collapsin response mediator protein-1 (CRMP-1) transcriptional regulatory nucleic acid sequences
2	20050224	70	US 20050043507 A1	Acyl-nucleotide probes and methods of their synthesis and use in proteomic analysis
3	20040715	366	US 20040139500 A1	Plastid division and related genes and proteins, and methods of use
4	20040610	22	US 20040110177 A1	Method for identifying functional nucleic acids
5	20040506	36	US 20040087784 A1	Neuronal serine-threonine protein kinase
6	20030508	61	US 20030087411 A1	Death associated kinase containing ankyr in repeats (DAKAR) and methods of use
7	20030424	20	US 20030077624 A1	Collapsin response mediator protein-1
8	20040803	65	US 6770477 B1	Differentially expressed genes associated with HER-2/neu overexpression

	Issue Date	Pages	Document ID	Title
1	20030508	61	US 20030087411 A1	Death associated kinase containing ankyr in repeats (DAKAR) and methods of use

	Issue Date	Pages	Document ID	Title
1	20050317	23	US 20050059092 A1	Alzheimer's disease diagnosis based on mitogen-activated protein kinase phosphorylation
2	20050217	21	US 20050037987 A1	Methods of identifying kinases and uses thereof
3	20041014	103	US 20040203097 A1	Kinases and phosphatases
4	20040701	105	US 20040126762 A1	Novel compositions and methods in cancer
5	20040610	121	US 20040110180 A1	Kinases and phosphatases
6	20040429	84	US 20040081983 A1	Kinases and phosphatases
7	20040422	151	US 20040077044 A1	Kinases and phosphatases
8	20040401	18	US 20040063119 A1	Analysis and modification of gene expression in marine invertebrate cells
9	20040325	81	US 20040058426 A1	Human kinases
10	20040318	144	US 20040053394 A1	Human kinases
11	20040226	152	US 20040038881 A1	Human kinases
12	20040205	144	US 20040023242 A1	Human kinases
13	20040129	112	US 20040018185 A1	Human kinases
14	20031113	136	US 20030211093 A1	Human kinases

15	20031106	148	US 20030207299 A1	Human kinases

	Issue Date	Pages	Document ID	Title
16	20030918	57	US 20030176437 A1	Anti-inflammatory and protein kinase inhibitor compositions and related methods for downregulation of detrimental cellular responses and inhibition of cell death
17	20030828	18	US 20030162230 A1	Method for quantifying phosphokinase activity on proteins
18	20040831	93	US 6783969 B1	Cathepsin V-like polypeptides

	Issue Date	Pages	Document ID	Title
1	20040506	36	US 20040087784 A1	Neuronal serine-threonine protein kinase
2	20030918	33	US 20030176678 A1	Novel IFN receptor 1 binding proteins, DNA encoding them, and methods of modulating cellular response to interferons
3	20030918	57	US 20030176437 A1	Anti-inflammatory and protein kinase inhibitor compositions and related methods for downregulation of detrimental cellular responses and inhibition of cell death
4	20020829	33	US 20020119129 A1	Novel IFN receptor 1 binding proteins, DNA encoding them, and methods of modulating cellular response to interferons
5	20001212	111	US 6160106 A	Tumor suppressor genes, proteins encoded thereby and use of said genes and proteins
6	19991019	65	US 5968816 A	Tumor suppressor genes, proteins encoded thereby and use of said genes and proteins

	Issue Date	Pages	Document ID	Title
1	20041104	32	US 20040219569 A1	Gene identification method
2	20040617	41	US 20040116364 A1	Modulation of death-associated protein kinase 1 expression
3	20030925	141	US 20030181710 A1	Death domain-containing receptor polynucleotides, polypeptides, and antibodies
4	20030918	57	US 20030176437 A1	Anti-inflammatory and protein kinase inhibitor compositions and related methods for downregulation of detrimental cellular responses and inhibition of cell death
5	20030403	171	US 20030065156 A1	Novel human genes and gene expression products I
6	20020620	141	US 20020077458 A1	Death domain-containing receptor polynucleotides, polypeptides, and antibodies
7	20010717	381	US 6262333 B1	Human genes and gene expression products
8	20010703	10	US 6255293 B1	Prevention of metastasis with 5-aza-2'-deoxycytidine
9	20001212	111	US 6160106 A	Tumor suppressor genes, proteins encoded thereby and use of said genes and proteins

10	19991019	65	US 5968816 A	Tumor suppressor genes, proteins encoded thereby and use of said genes and proteins

	L #	Hits	Search Text
1	L1	6662	calmodulin
2	L2	354092	calcium
3	L3	2421	l1 same l2
4	L4	22346	kinase?
5	L5	601	l3 same l4
6	L6	8	"DRP-1"
7	L7	1	"DAP kinase related protein?"
8	L8	23456	apoptosis or "cell adj death"
9	L9	18	l5 same l8
10	L10	335	KIMCHI
11	L11	608	l5 or l6
12	L12	6	l10 and l11
13	L13	60	l8 and l10
14	L14	10	l1 and l13